EPFL

Neuro X Institute

Non-invasive deep brain stimulation

Nx-436

'Advanced methods for human neuromodulation'

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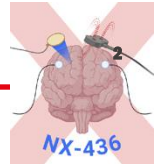
Overview



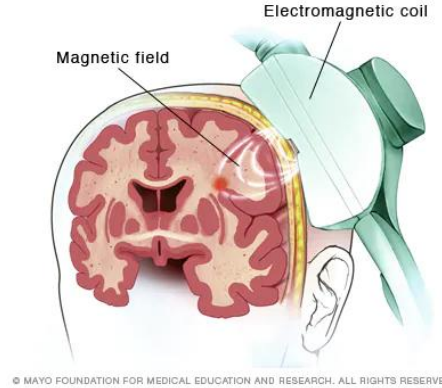
Non-invasive deep brain stimulation

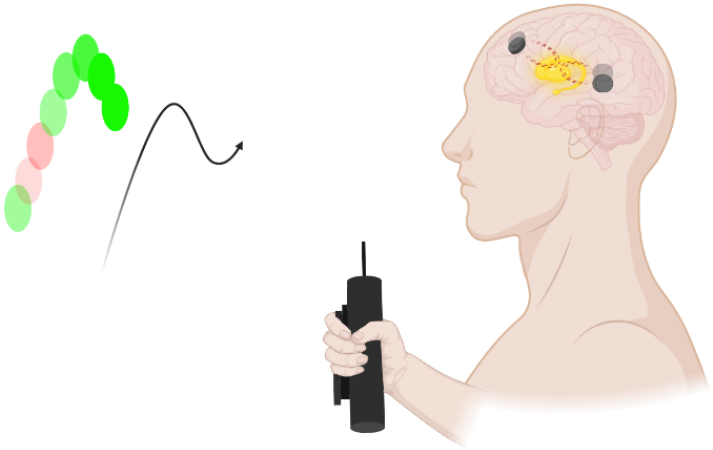
- 2 methods that will be discussed
  - Deep TMS
  - Transcranial temporal interference stimulation (tTIS)
- Concepts and Mechanims of these methods

Applications

Challenges/Limitations

Optimization



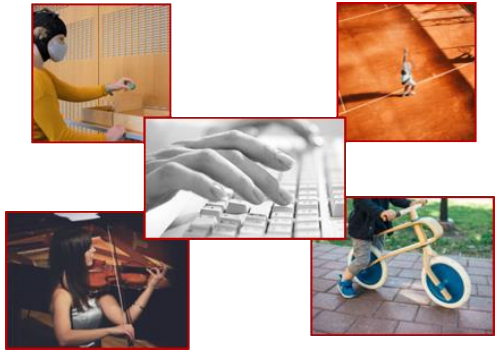


Non-invasive deep brain stimulation

deep TMS

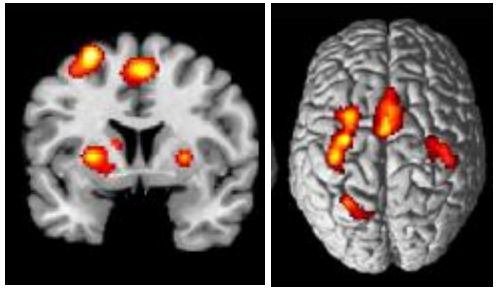
transcranial temporal interference stimulation (tTIS)

Neuromodulation of deep brain structures

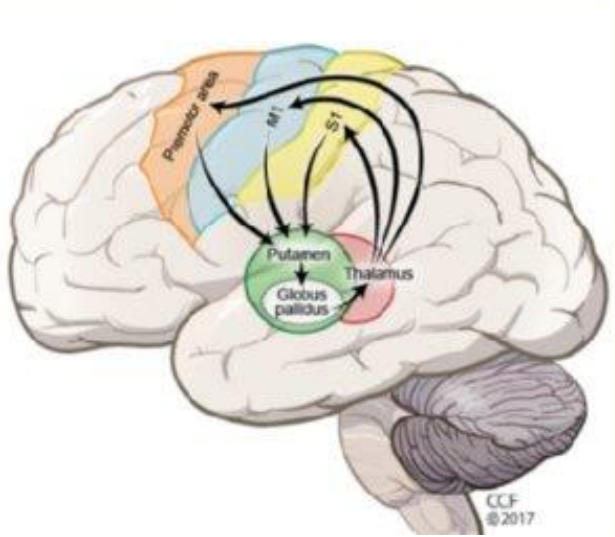


Motor Learning

Memory



Motor, cognitive functions – cortico-subcortical processing



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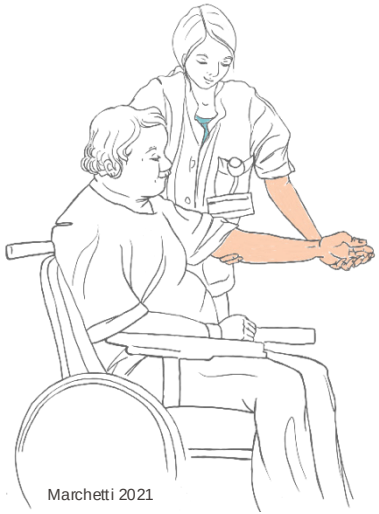
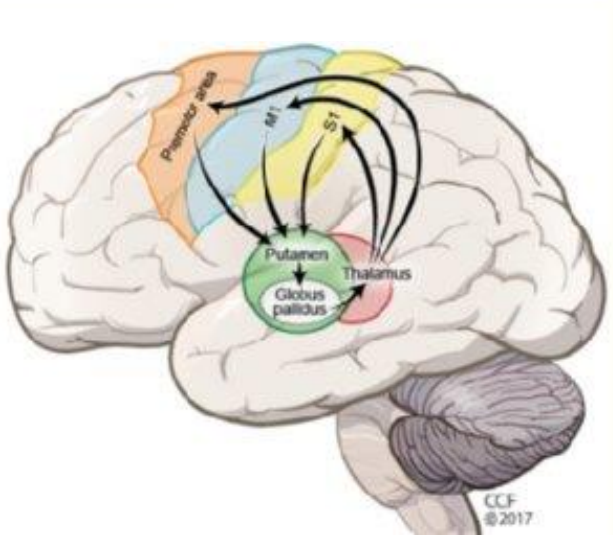


Marchetti 2021

Stroke

Parkinson's



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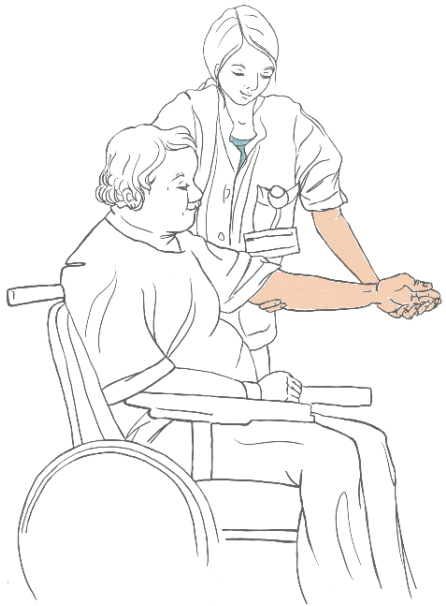
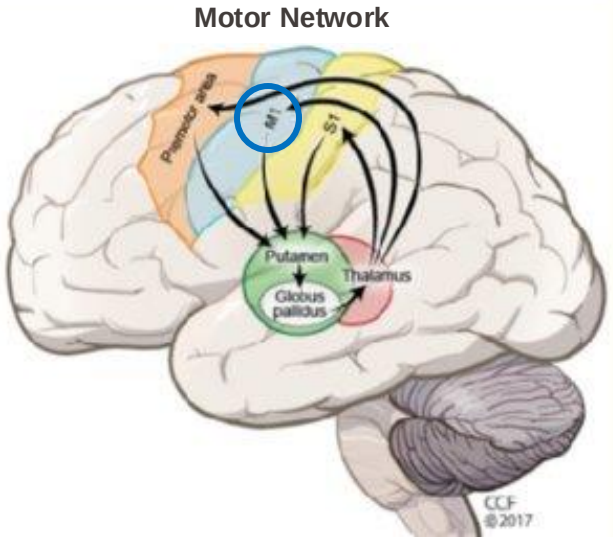


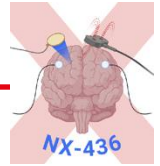
Non-invasive brain stimulation



e.g., Maceira-Elvira *et al.* 2022 Sci Adv, Nat Nsc; Zimerman *et al.* 2013 Ann Neurol; Zimerman *et al.* 2014 Cerebral Cortex; Nitsche *et al.* 2000 J Physiol

Stroke recovery: Hummel et al. 2005 Brain; Hummel & Cohen 2006 Lancet Neurology

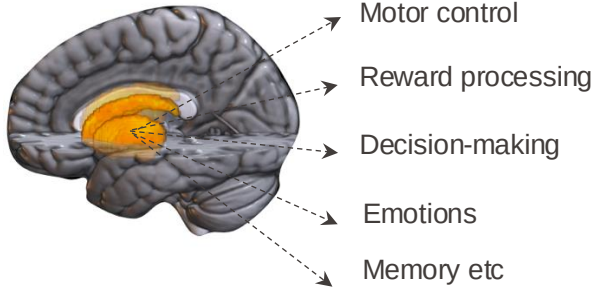
Neuromodulation of deep brain structures



Deep brain regions are altered in many **neuro-psychiatric disorders**:

e.g., **striatum, hippocampus, thalamus, DLPFC**

- Stroke
- Apathy
- Parkinsons' disease
- Epilepsy
- Dementia…



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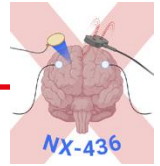

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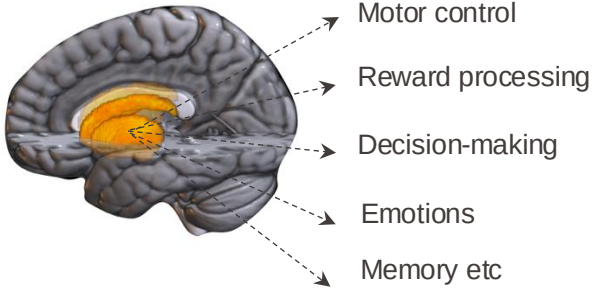
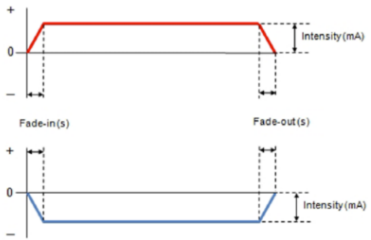


Challenge: focal, non-invasive deep brain stimulation is not possible with conventional approaches due to steep depth-focality trade-off

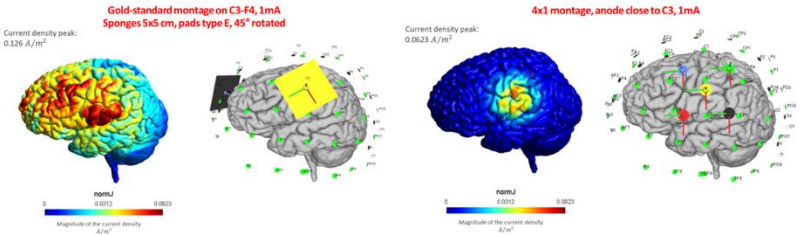
Neuromodulation by NIBS

transcranial Direct Current Stimulation (tDCS)

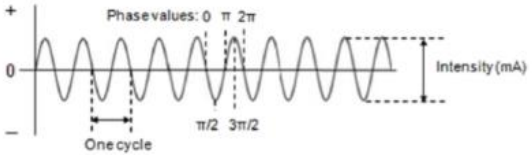


Anodal tDCS

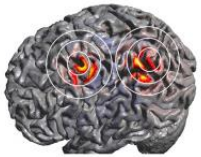
Cathodal tDCS

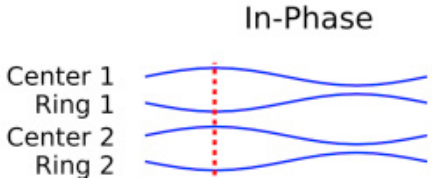


transcranial Alternating Stimulation (tACS)

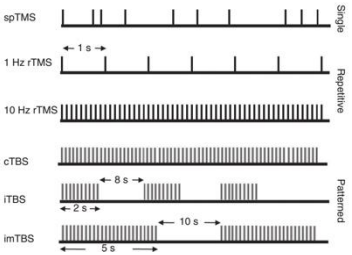


tACS





transcranial Magnetic Stimulation (TMS)



For review see e.g., Hummel & Cohen 2006; Wessel *et al.* 2015; Saturnino *et al.* 2017

Neuromodulation by NIBS

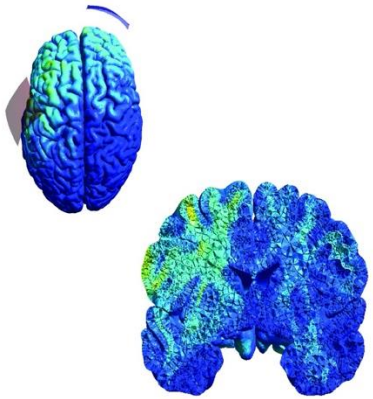
transcranial Direct Current Stimulation (tDCS)

transcranial Alternating Stimulation (tACS)

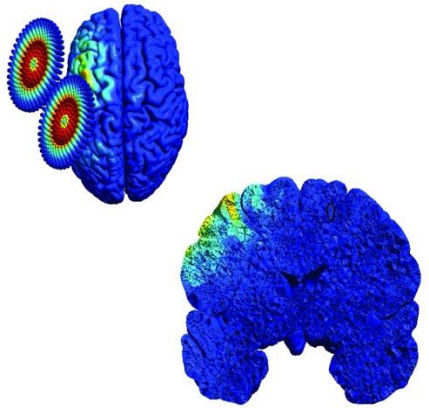
transcranial Magnetic Stimulation (TMS)

Depth-focality trade-off

Conventional tES



TMS



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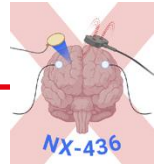

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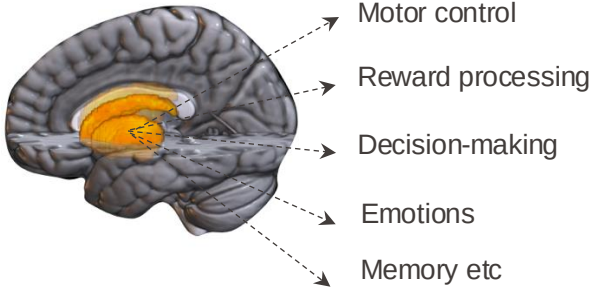
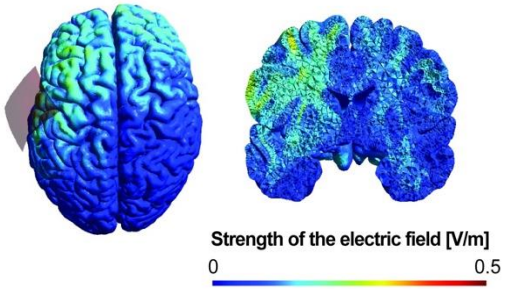
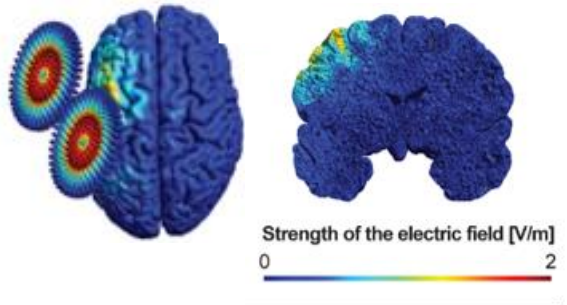


Challenge: focal, non-invasive deep brain stimulation is not possible with conventional approaches

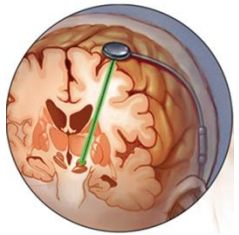
Conventional tES



TMS

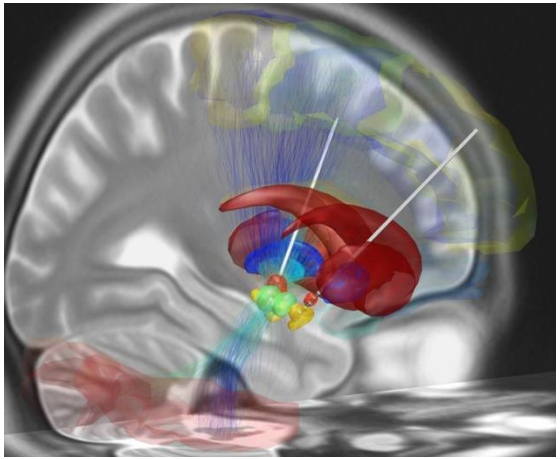


Deep brain stimulation is so far **limited to invasive methods**



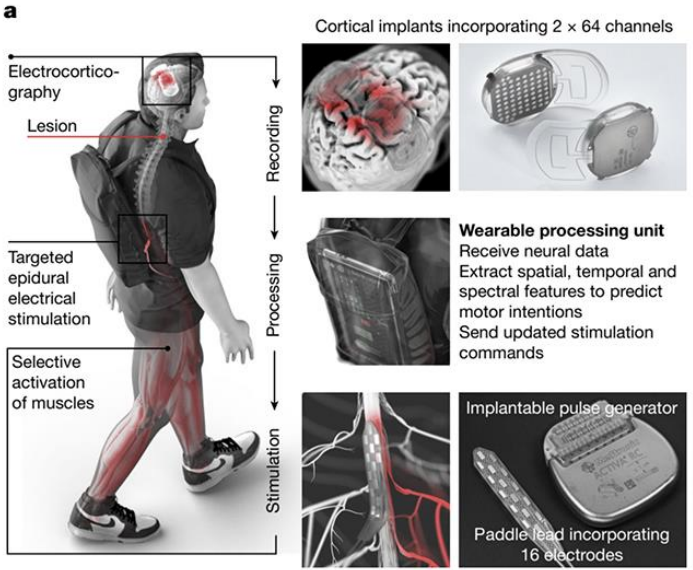
Invasive CNS stimulation

(Adaptive) Deep Brain Stimulation



For review e.g., Marcegli *et al.* (2024) JNE

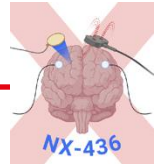
Brain Spine Bridge – Spinal Cord Stimulation



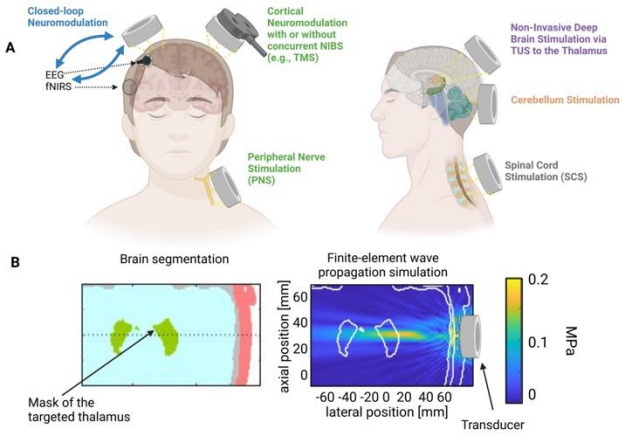
Lorach *et al.* (2023) Nature

- Effective, excellent for 24/7 use
- Invasive with respective side effects
- Costly
- Not accessible for a large part of patients (e.g., only 2-4% of PD patients have DBS treatment)
- Not for responder, non-responder testing (personalization)

Non-invasive Deep brain stimulation – novel technology

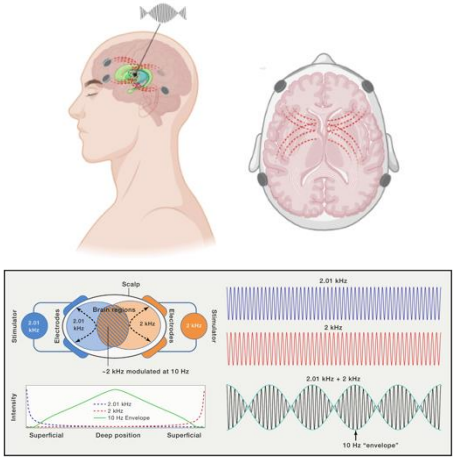


transcranial focused Ultrasound (tUS)



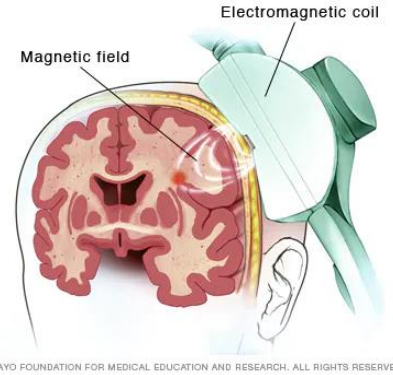
For review e.g., Yüksel et al. *IEEE EMBS* 2024

transcranial Temporal Interference electrical Stimulation (tTIS)

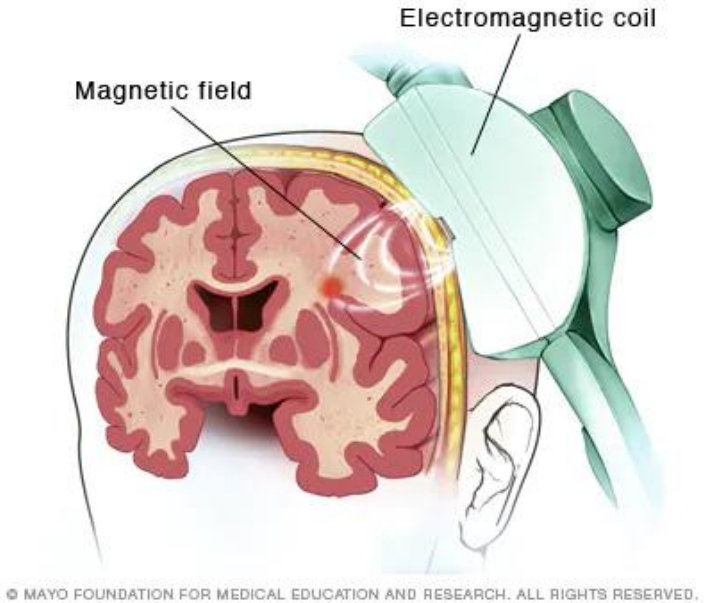


Hummel & Wessel *Nature Review Neurology* 2024
Vassiliadis et al. *Nature Human Behavior* 2024
Beanato et al. *Science Advances*, 2024
Wessel, Beanato et al. *Nature Neuroscience* 2023
Violante et al. *Nature Neuroscience* 2023
Grossman et al. *Cell* 2017

Deep TMS



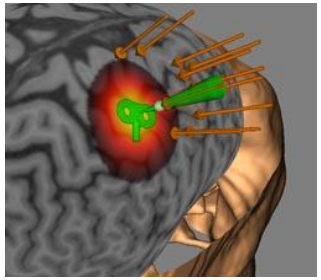
Bersani et al. *Eur Psychiatry* 2013
Di Passa et al. *J Psychiatr Res.*2024

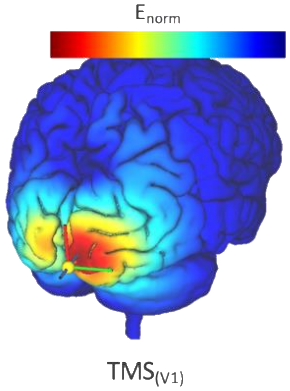


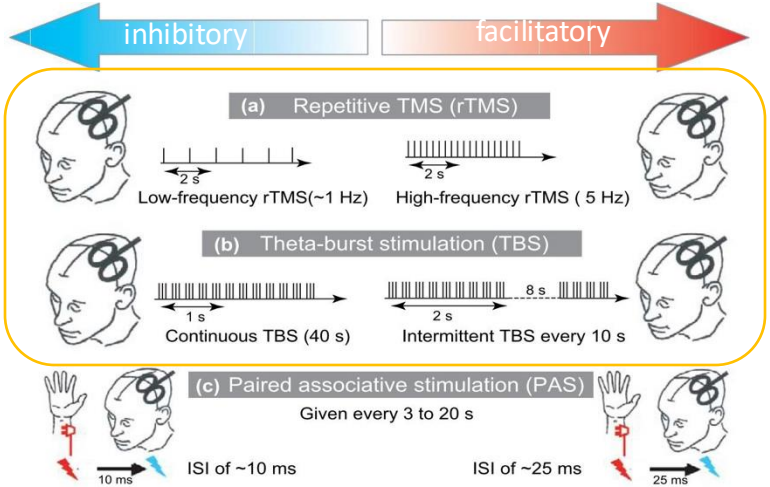
deep TMS

TMS

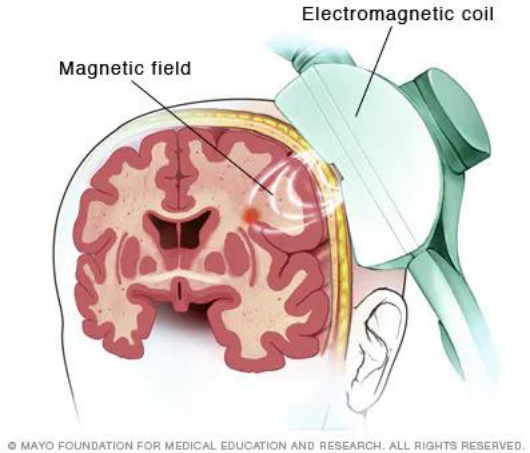
Transcranial Magnetic Stimulaton (TMS)

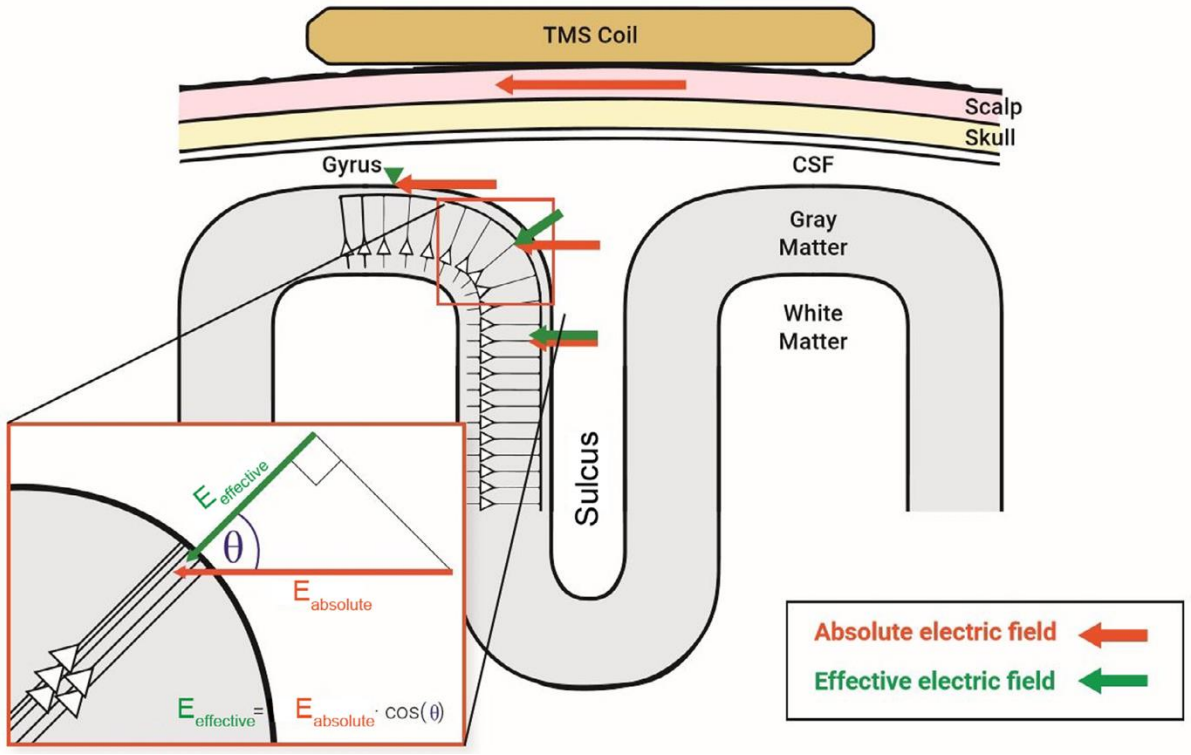






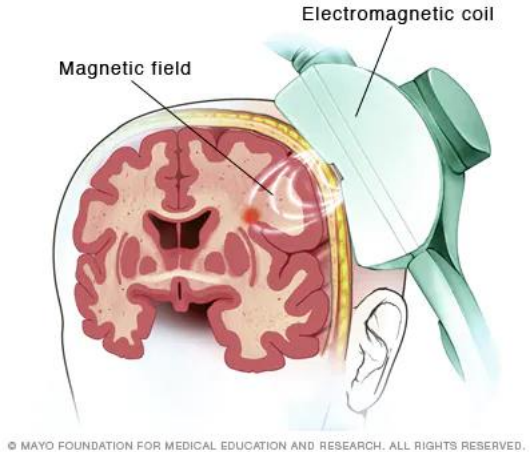
Deep TMS

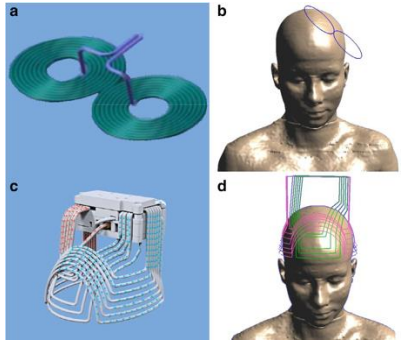


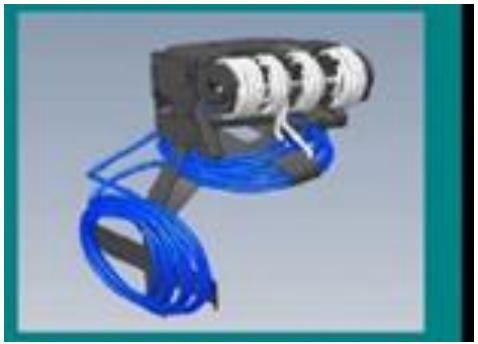


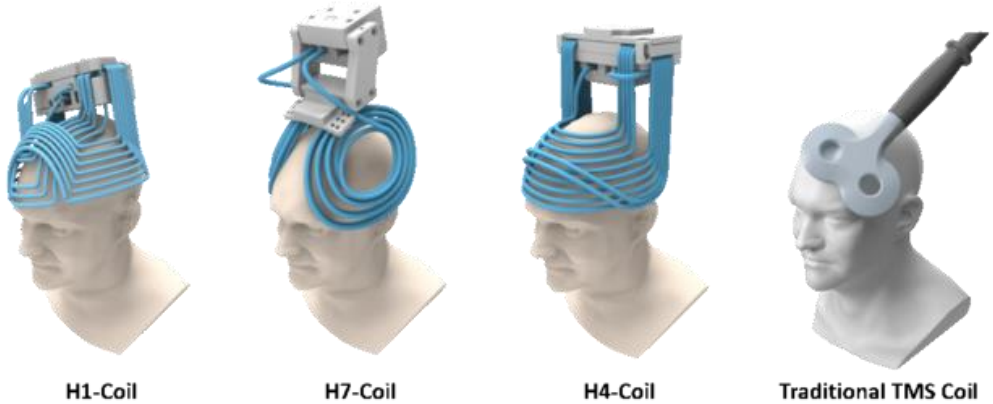
Zibma *et al*., 2021, Pell *et al*., 2023,

Deep TMS



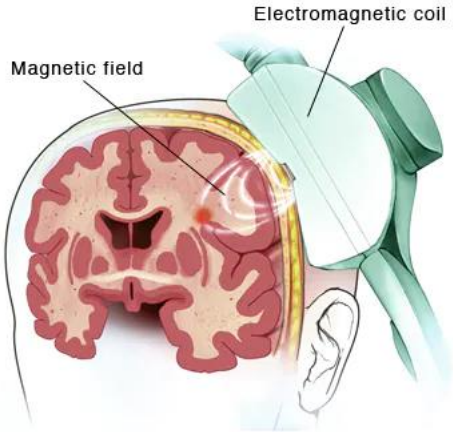


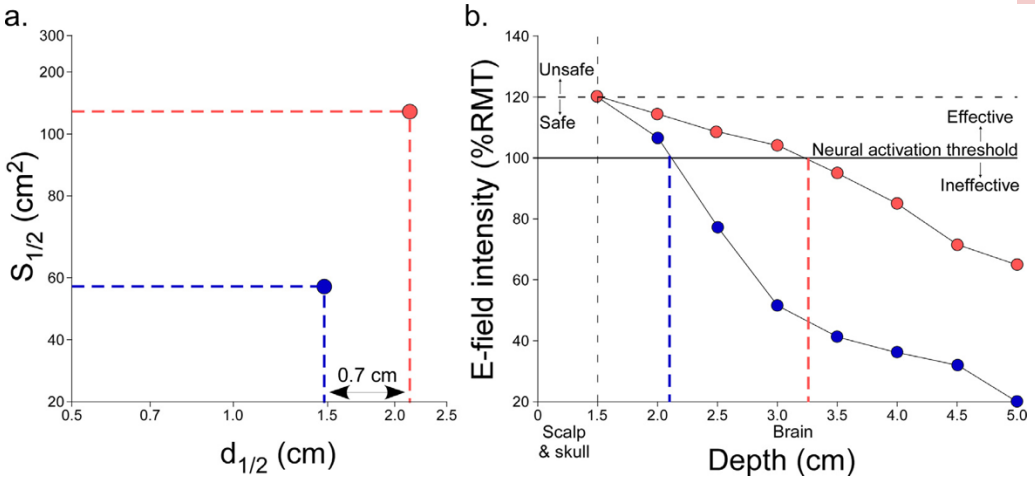


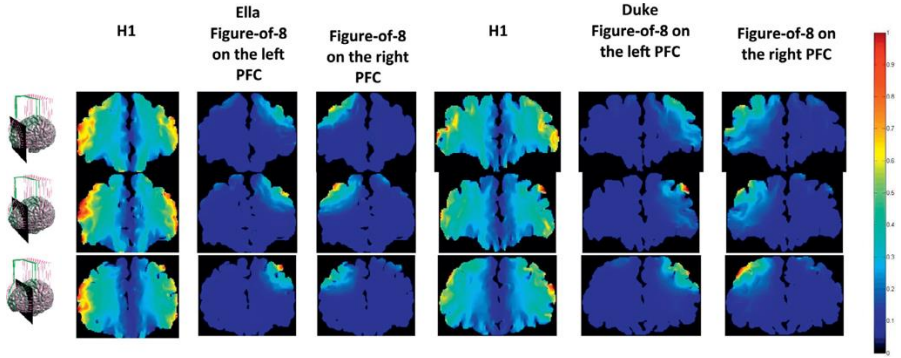


Zibma *et al*., 2021, Pell *et al*., 2023, https://www.brainsway.com

Deep TMS







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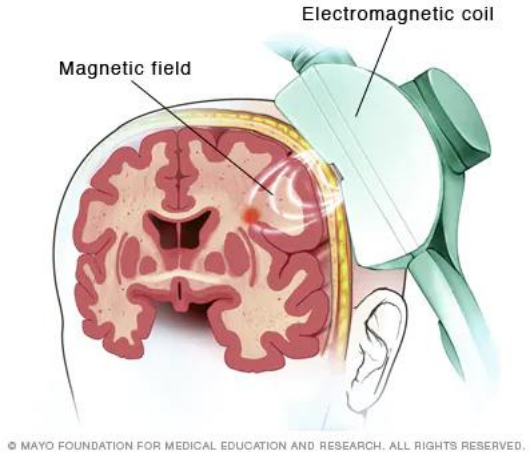

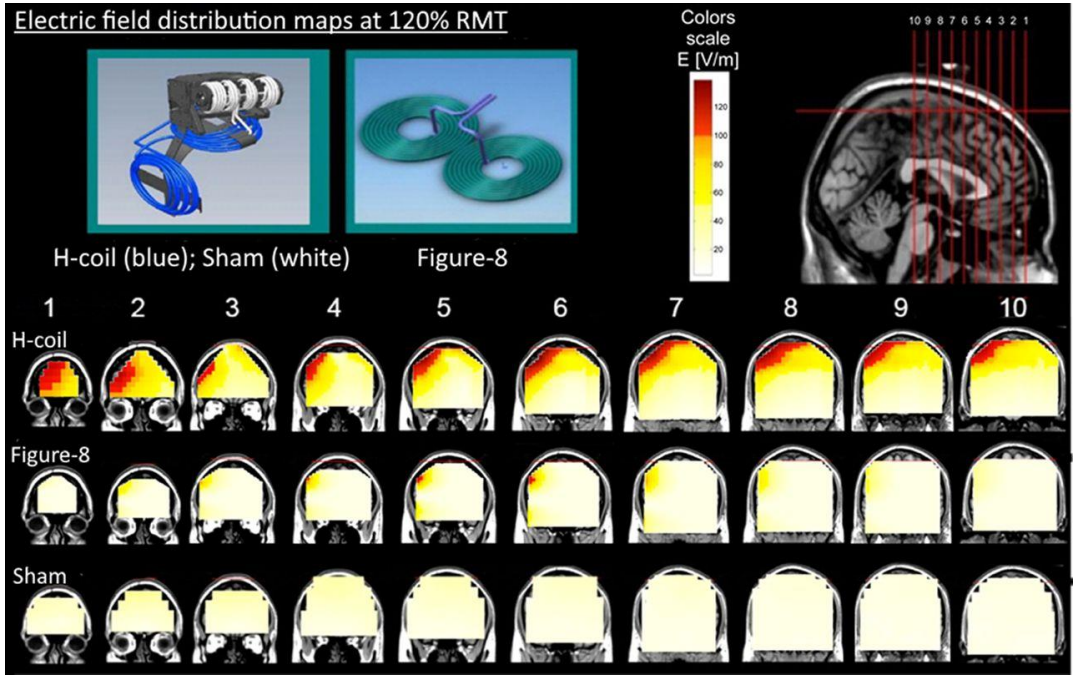

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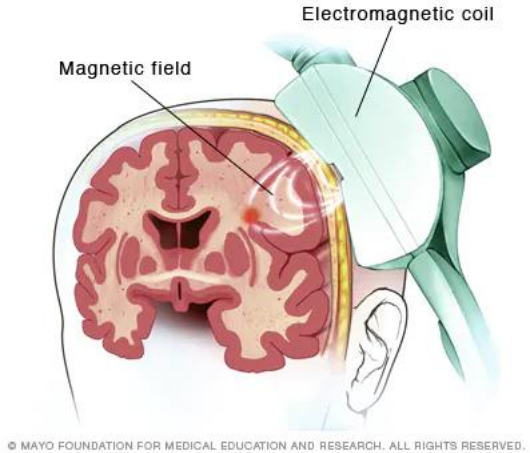

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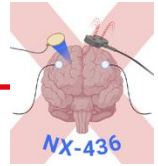
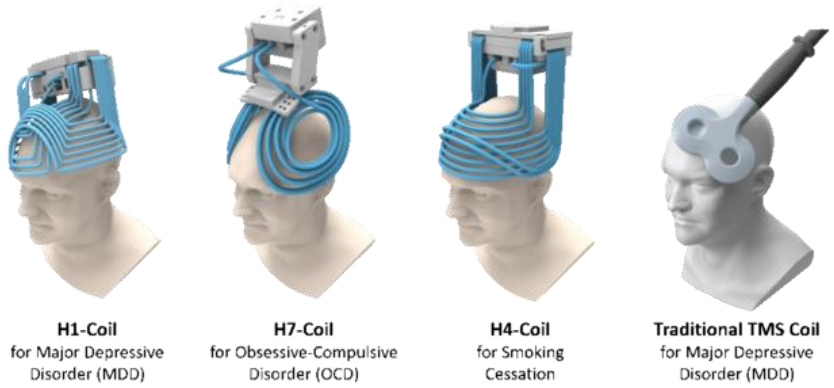


Deep TMS has been CE-marked to treat:

Patients diagnosed with major depressive disorder.
Patients diagnosed with obsessive-compulsive disorder.
Patients diagnosed with smoking addiction.
Patients diagnosed with Alzheimer's disease.
Patients diagnosed with autism.
Patients diagnosed with bipolar disorder.
Patients diagnosed with chronic pain.
Patients diagnosed with multiple sclerosis (MS).
Patients diagnosed with Parkinson's disease.
Patients diagnosed with post-stroke rehabilitation.
Patients diagnosed with post-traumatic stress disorder (PTSD).
Patients diagnosed with negative symptoms of schizophrenia



H1-Coil
for Major Depressive Disorder (MDD)

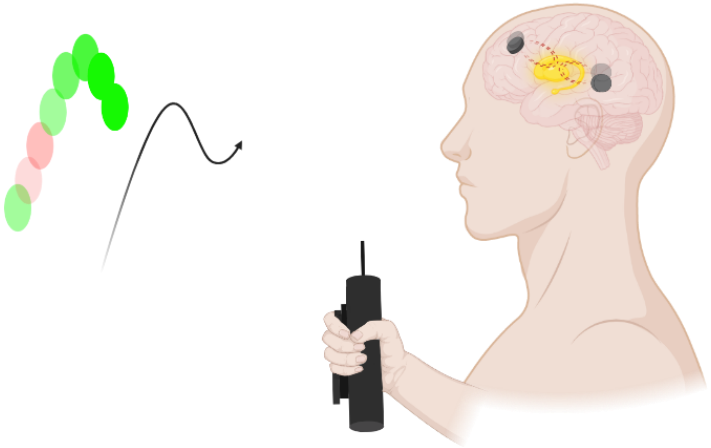
H7-Coil
for Obsessive-Compulsive Disorder (OCD)

H4-Coil
for Smoking Cessation

Traditional TMS Coil
for Major Depressive Disorder (MDD)

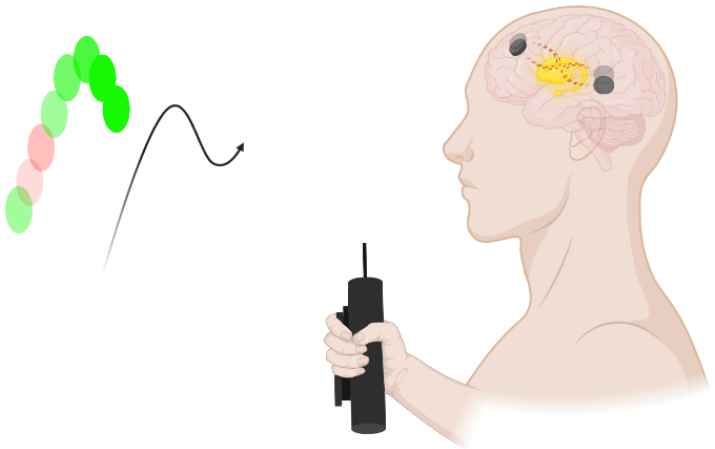
- **Deep TMS by means of H-Coils allows to reach deeper (cortical) structure**
- **Lower focality then classical Figure of 8 coils**
- **Based on special coil architecture**
- **Improves treatment effects**

- **However, still limited to the Cortex!**



tTIS

Transcranial temporal interference electrical stimulation (tTIS)

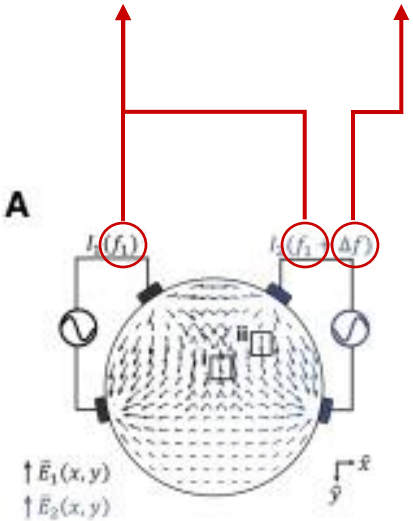


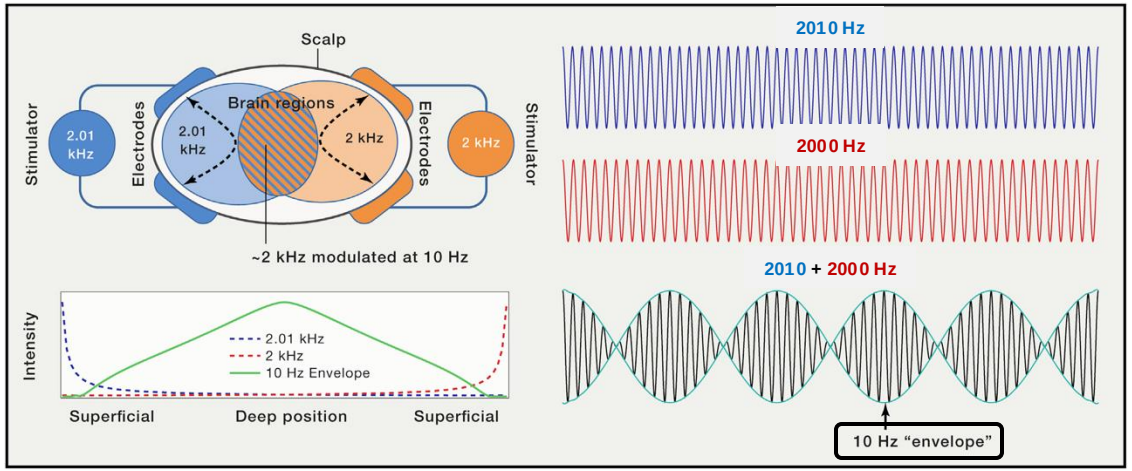
Wessel*, Beanato* *et al.,* 2023, *Nature Neuroscience;* Vassiliadis *et al.*, 2024 *Nature Human Behaviour,* Beanato, Moon *et al.* 2024 *Science Advances*; Vassiliadis et al. 2024 *JNE*; Yang et al. 2024 *MDS*; Violante *et al.* 2023 *Nature Neuroscience*

transcranial Temporal Interference Stimulation (tTIS)

High frequency outside neural operation

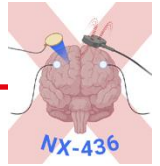
Frequency recruiting neurons

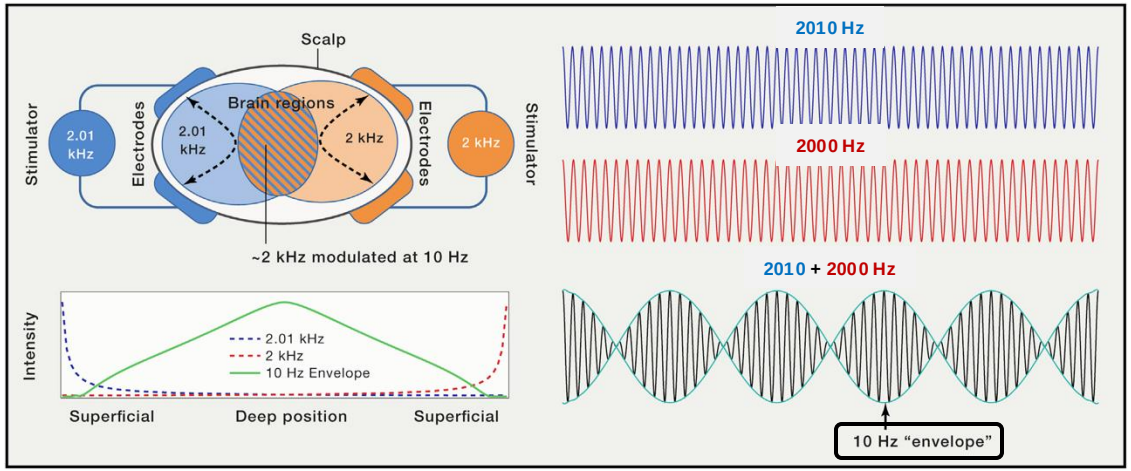


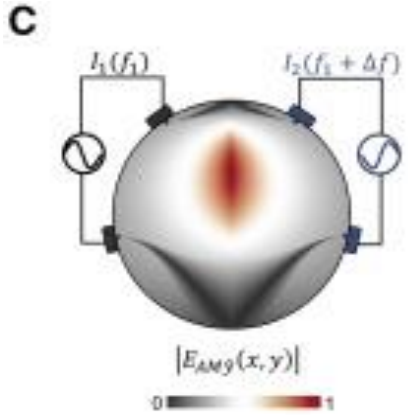


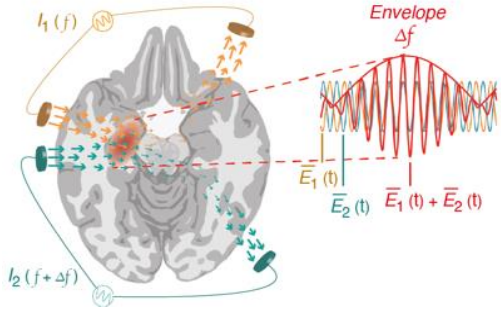
Grossman *et al.*, Cell 2017; Dmochowsk *et al*. 2017 Cell

transcranial Temporal Interference Stimulation (tTIS)



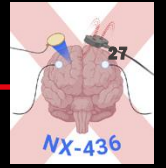


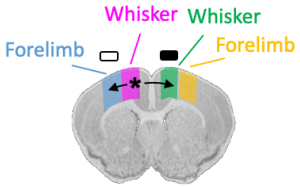




Grossman *et al.*, Cell 2017; Dmochowsk *et al*. 2017 Cell

tTIS – animal /cadaver work



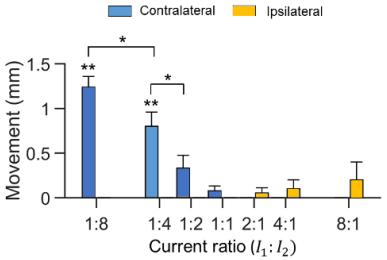


Ipsilateral (to I_1)

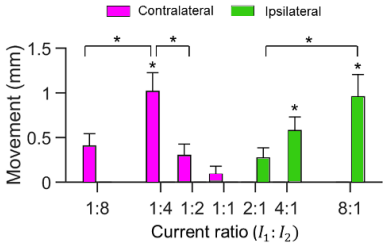
Contralateral (to I_1)

Movement

Mean (± s.e.m) Forepaw Movement

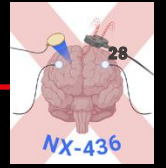


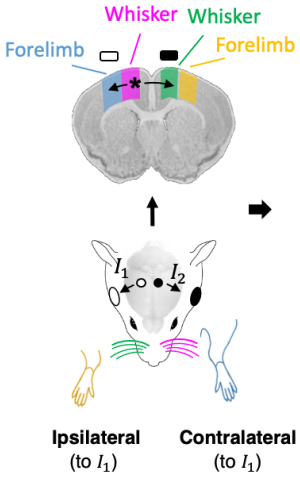
Mean (± s.e.m) Whisker Movement



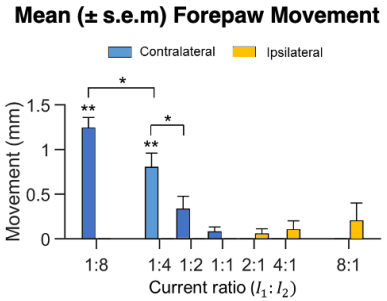
Grossman *et al.*, Cell 2017

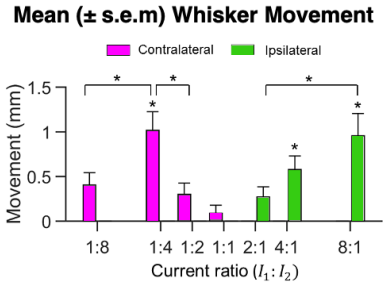
tTIS – animal /cadaver work

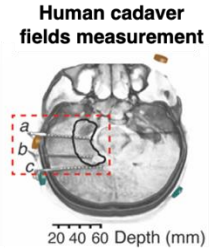




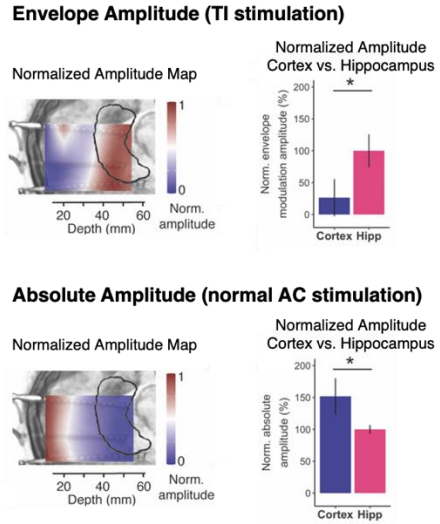
➡ Movement







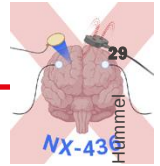
➡



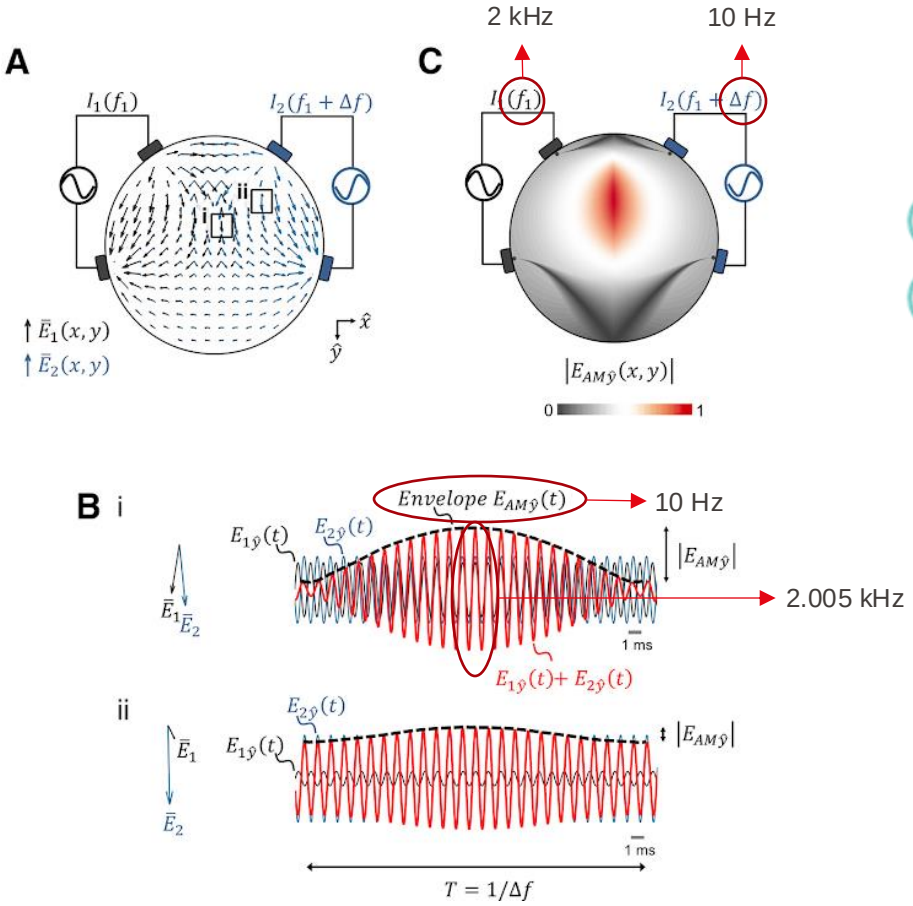
Grossman et al., Cell 2017

Violante *et al.*, bioRxiv 2022

Transcranial Temporal Interference Stimulation (tTIS)

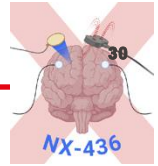


Friedhelm C. Hummel



- Good **spatial** resolution
- Able to **reach deep brain structures**

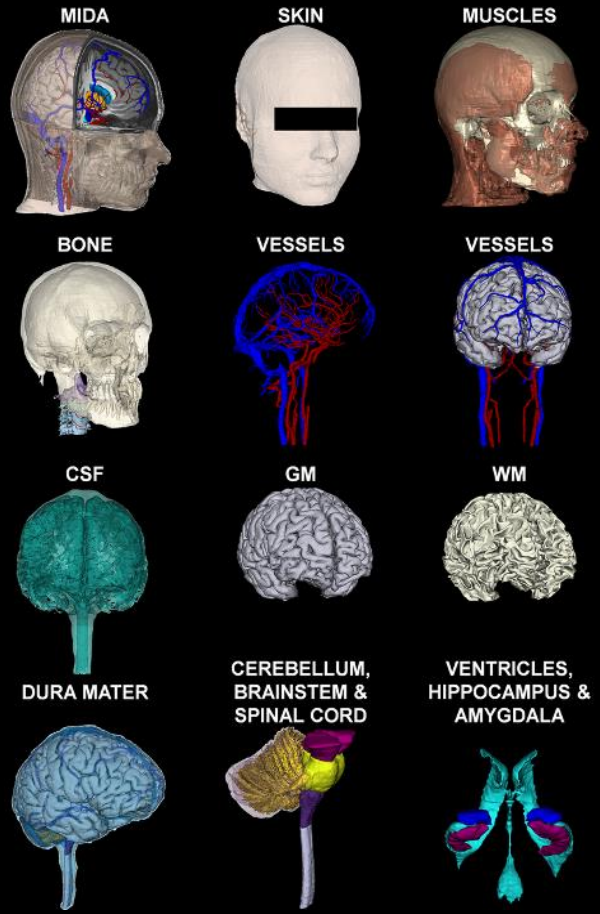
Grossman et al., Cell 2017

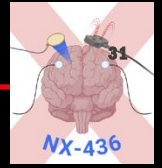


Questions to solve

Localization
Stimulation parameters
Focality of stimulation effects
Validation of stimulation effects

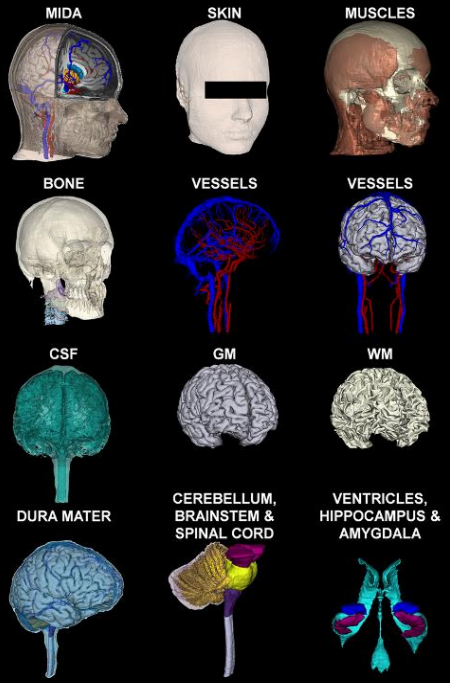
Simulations – anatomical model

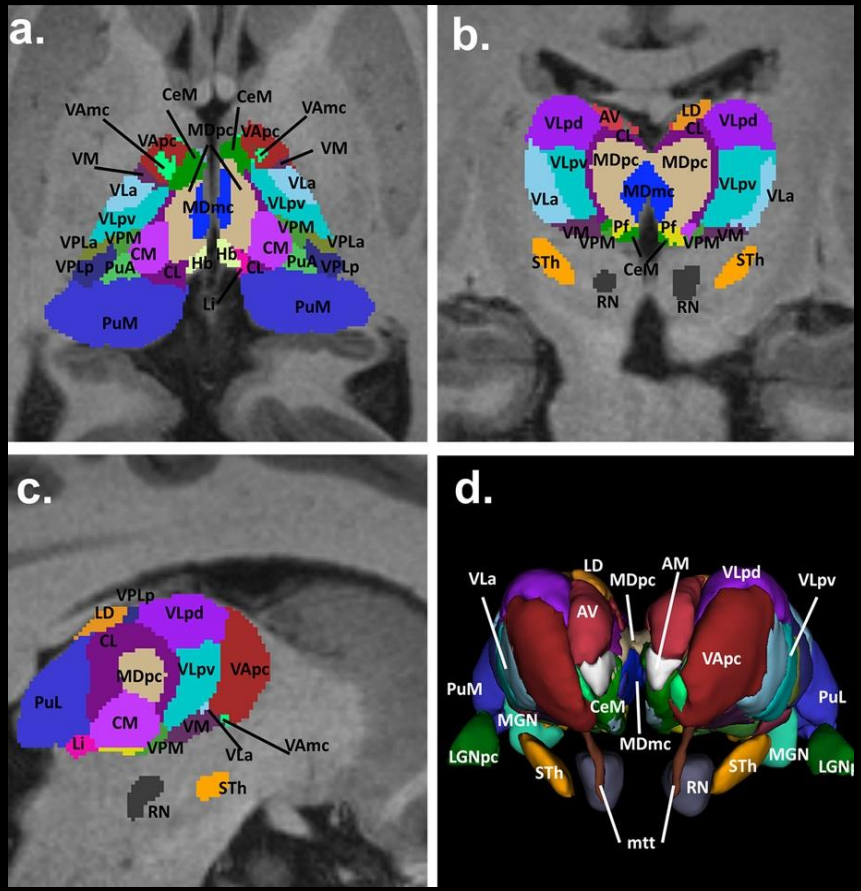


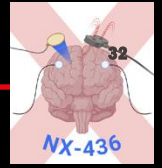


Iacono MI *et al.* (2015).: PLoS one **10**(4): e0124126

Simulations – anatomical model

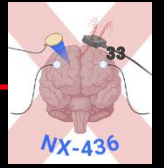


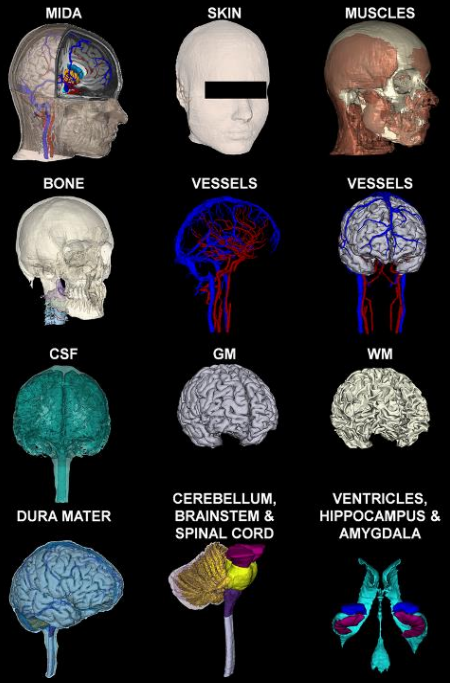




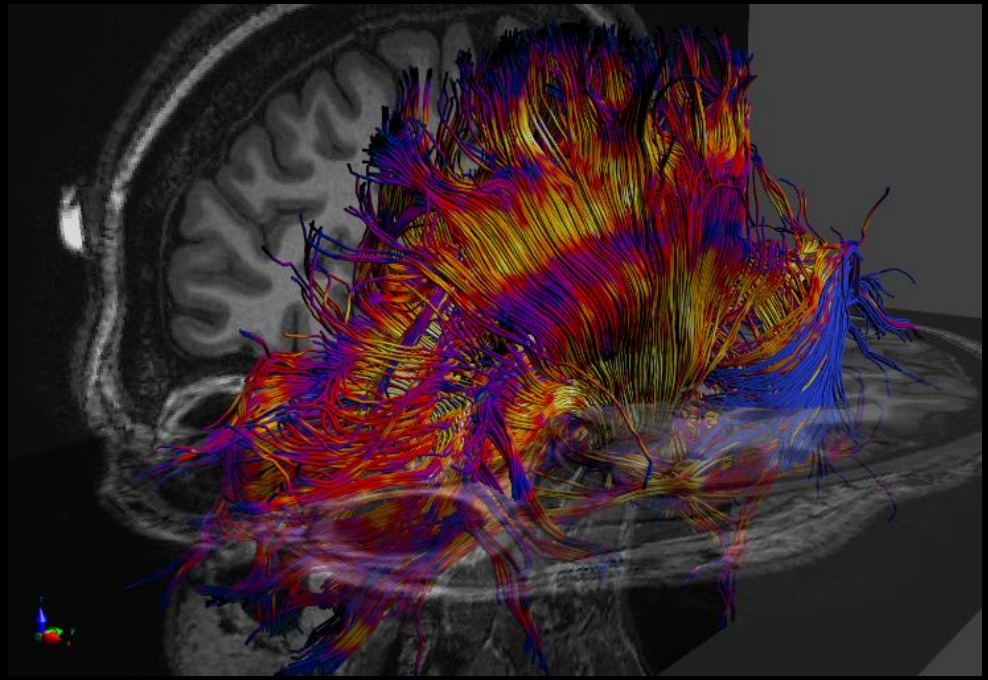
Iacono MI *et al.* (2015).: PLoS one **10**(4): e0124126

Simulations – anatomical model





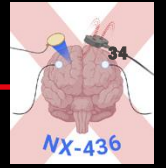
Further informing the model



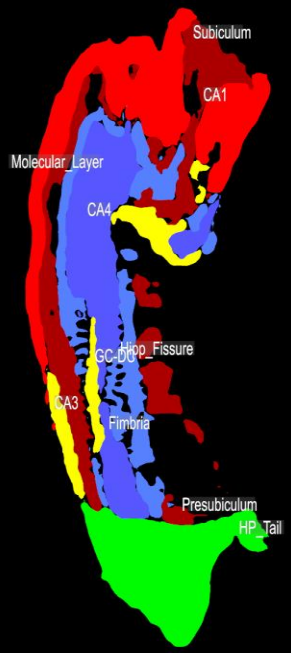
Diffusion tensor imaging (DTI) to obtain information on tissue anisotropy and fiber orientation

Iacono MI *et al.* (2015).: PLoS one **10**(4): e0124126

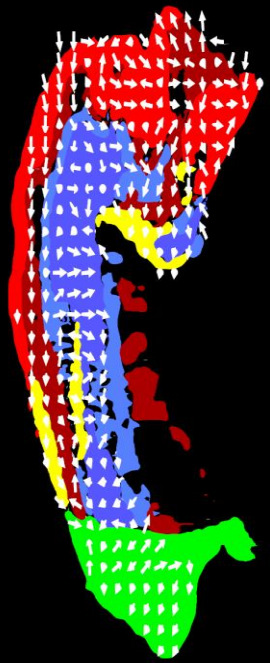
Simulations – anatomical model



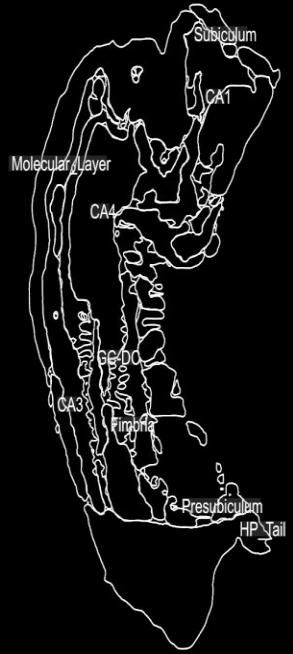
Hippocampus simulations (MIDA model)



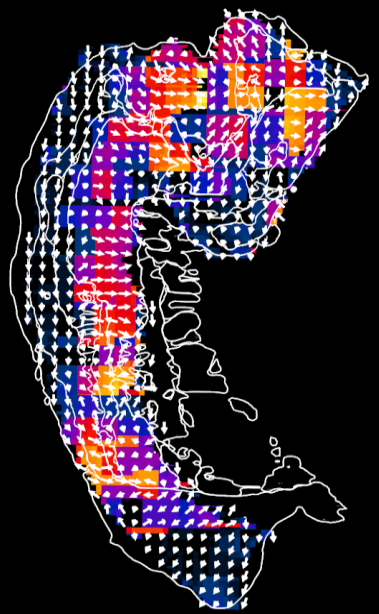
Labels



DTI Directions

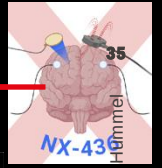


Contours

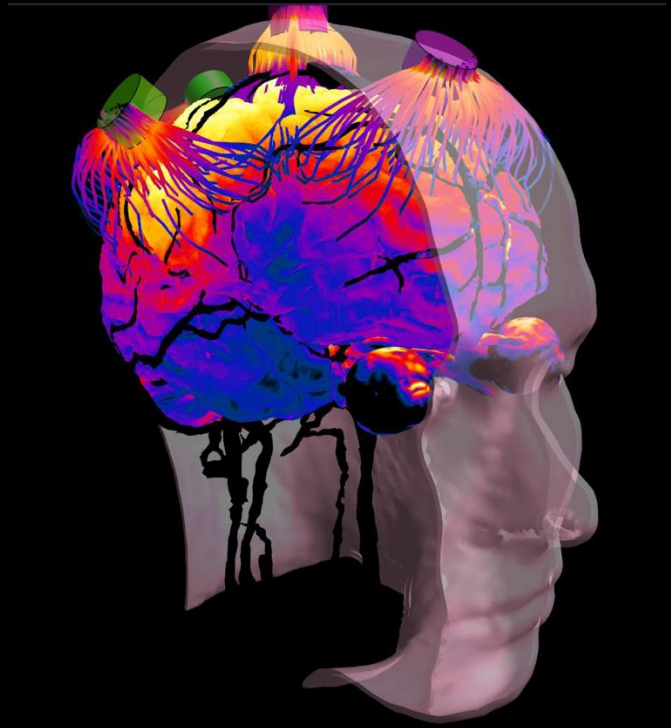


TI stimulation

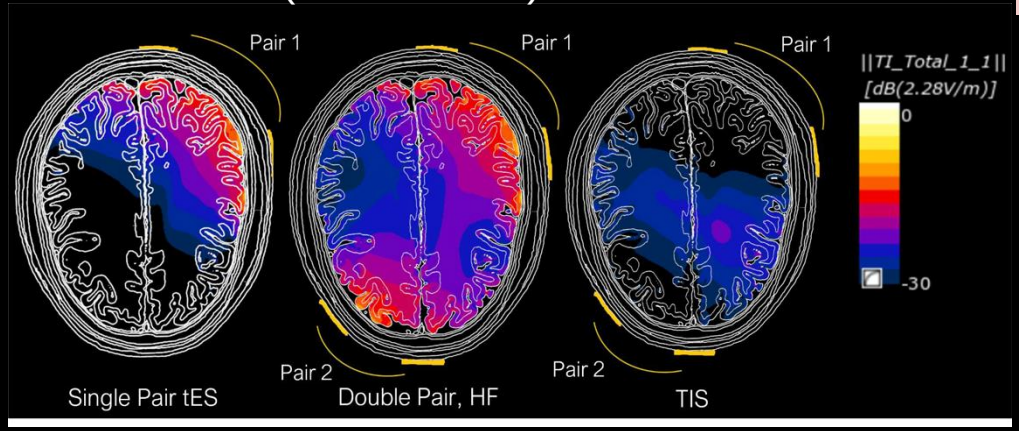
Courtesy E. Neufeld

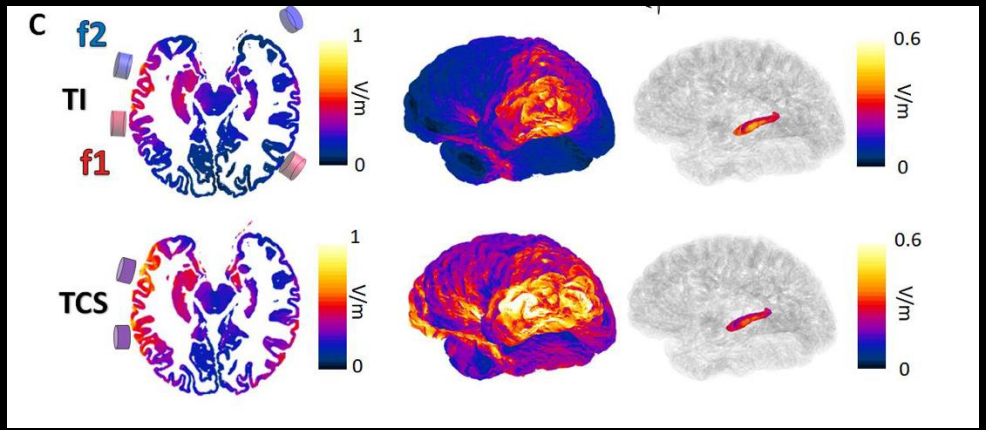


Whole brain simulations (MIDA model)



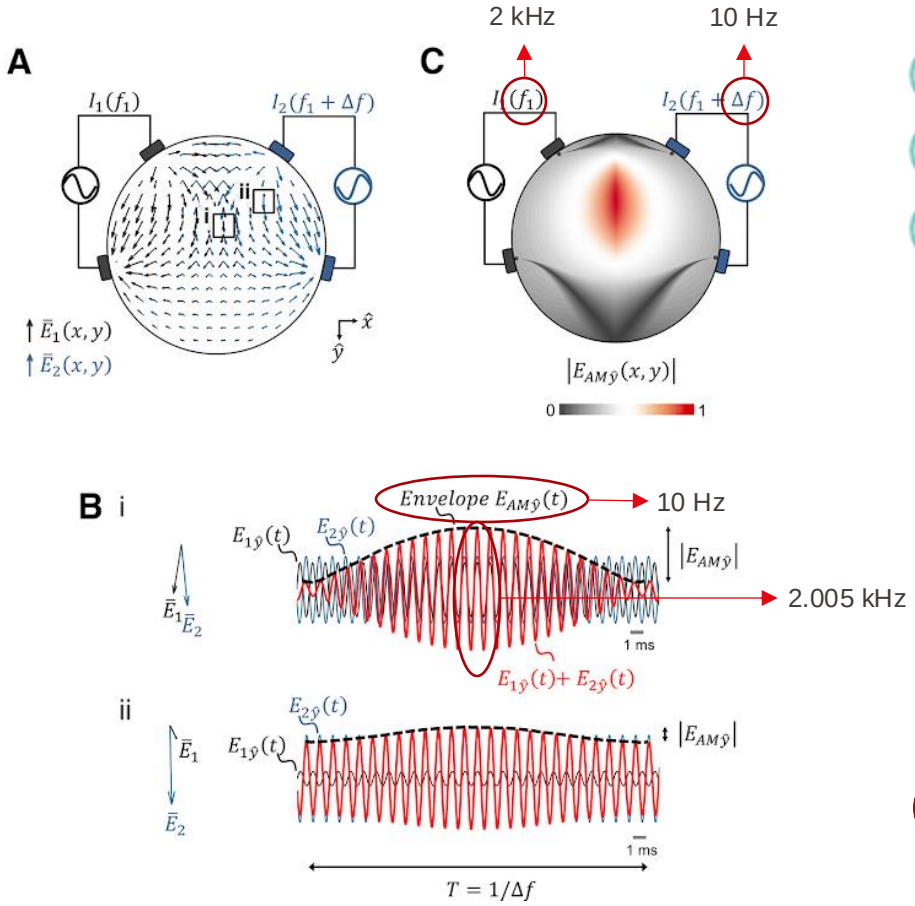
High resolution head model (MIDA, SIM-4-Life) in cooperation with E. Neufeld (IT'IS, ETH Zürich)





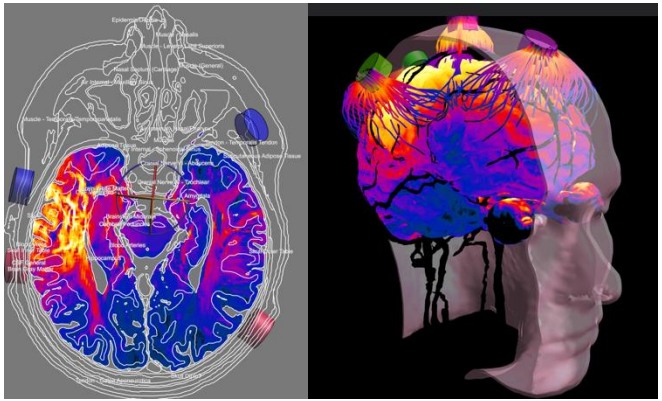
Courtesy E. Neufeld

tTIS – human translation?



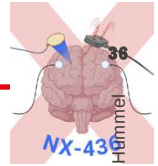
Grossman *et al.*, Cell 2017

- Good **spatial** resolution
- Able to **reach deep brain structures**
- **Simulations** crucially important for targeting

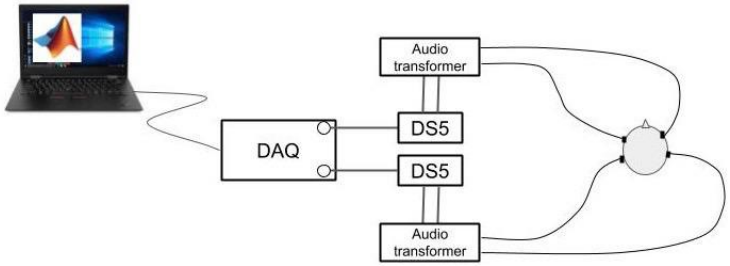


Courtesy E. Neufeld

? **Feasible, effective** in humans



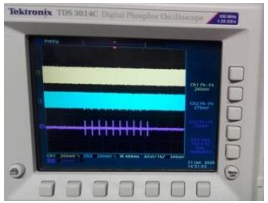
Friedhelm C. Hummel

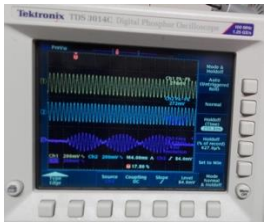


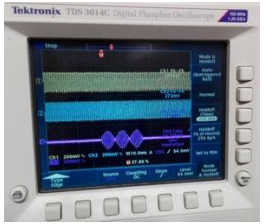
Details component parts:

- DS5: Digitimer DS5 Isolated Bipolar Current Stimulator
- DAQ: National Instruments DAQ model USB-6216 (16-Bit, 400 kS/s, BNC, Bus-Powered)
- Audio transformer: Hammond Manufacturing 1140-LN-B.

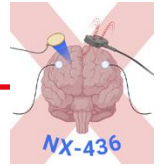
Theta bursts waveforms







- 2kHz carrier frequency,
- 10 bursts at 5Hz,
- 3 pulses at 100Hz



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Molecular Psychiatry

ARTICLE

Check for updates

Placebo effects and neuromodulation for depression: a meta-analysis and evaluation of shared mechanisms

Matthew J. Burke[1,2,3,12]✉, Sara M. Romanella[3,4,12], Lucia Mencarelli[3,4], Rachel Greben[2], Michael D. Fox[3,5,6], Ted J. Kaptchuk[7], Alvaro Pascual-Leone[8,9,10] and Emiliano Santarnecchi[3,11]✉

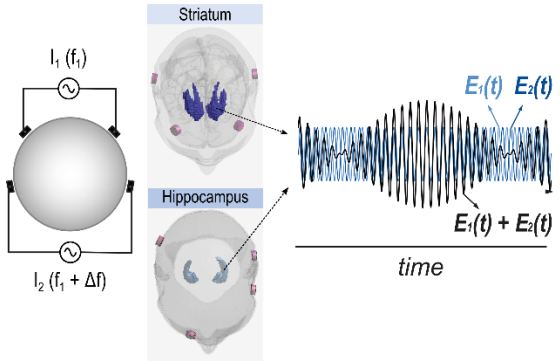
Blinding – perceived sensations

A.

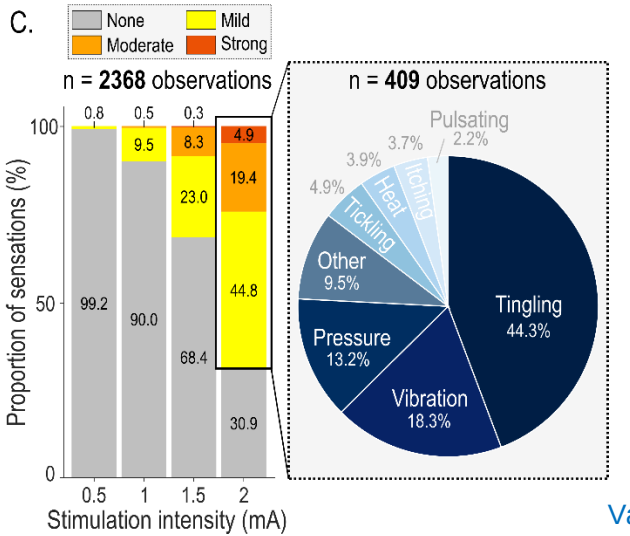
Exp number	Subject number	Target	Population	tTIS Type	Session number/exp	Session number total	Sensation data points at 2mA
1	15	Striatum	Young	iTBS/HF	4	59*	118
2	15	Striatum	Young	iTBS/HF	2	30	60
3	8	Striatum	Young	iTBS/cTBS/HF	3	24	72
4	24	Striatum	Young	20Hz/80Hz/Sham	1	24	72
5	15	Striatum	Older	iTBS/HF	2	30	60
6	30	Hippocampus	Young	iTBS/cTBS/HF or Sham**	1	30	90
7	15	Hippocampus	Older	cTBS/HF	2	30	60
8	15	Hippocampus	TBI	iTBS/Sham	2	30	60

Total:
- **119** participants
- **257** sessions
- **592** sensation data points at 2mA

B.

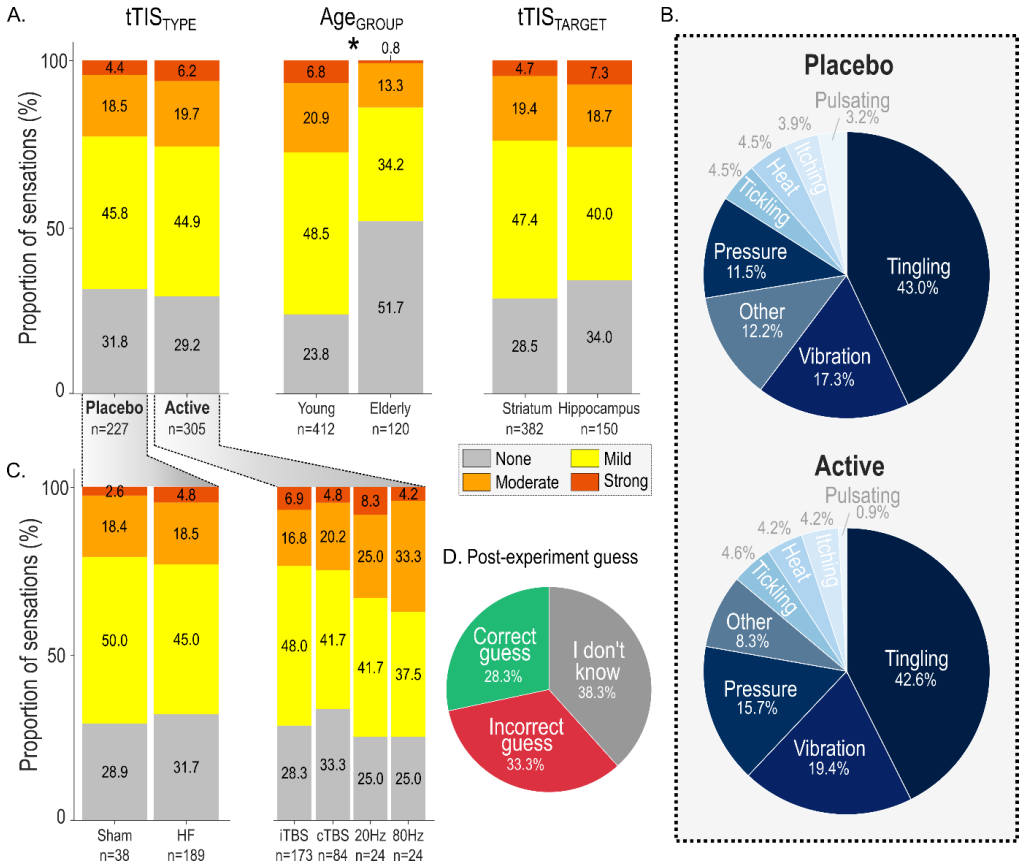


C.



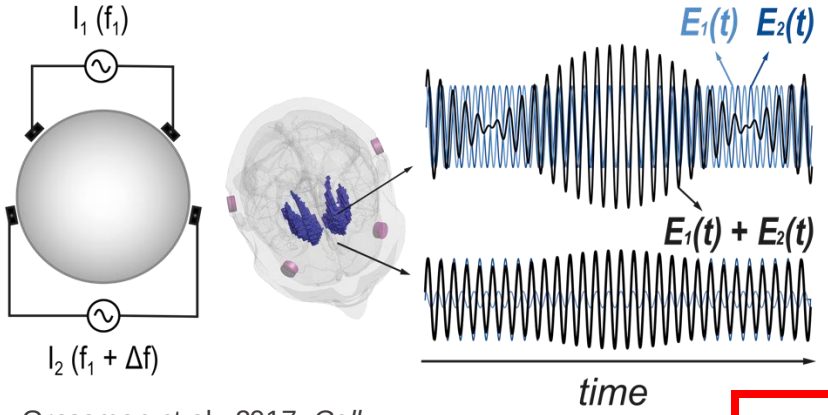
Vassiliadis *et al.*, JNE 2024

Blinding – perceived sensations



Vassiliadis *et al.*, JNE 2024

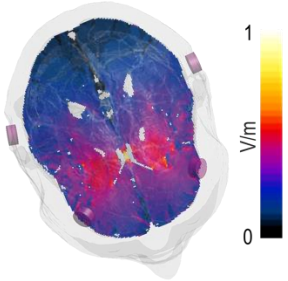
transcranial Temporal Interference Stimulation (tTIS)

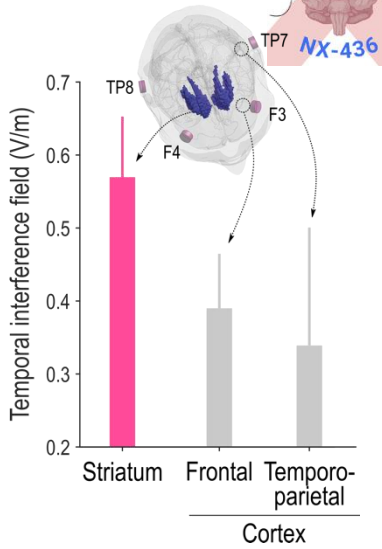


Grossman et al., 2017, *Cell*

First application of deep tTIS in humans

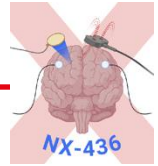
Simulations on high resolution head model (collab. Prof Neufeld)



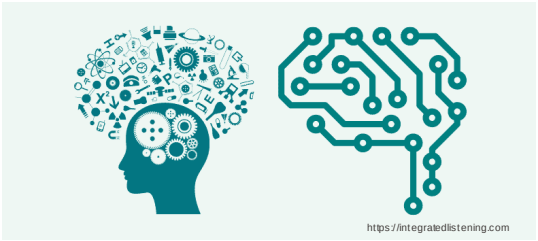


- Animal model validation (Grossman et al., 2017)
- Application on cortical structures in humans (Ma et al., 2021)
- Cadaver work (Violante et al., 2023)

Stimulation protocols - tTIS

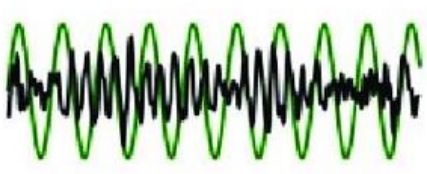


Neuroplasticity



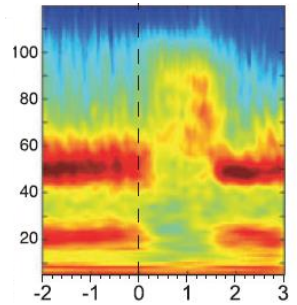
Wessel, Beanato *et al.* (2023) Nature Neuroscience
Beanato, Moon *et al.* (2024) Science Advances

Neuronal entrainment



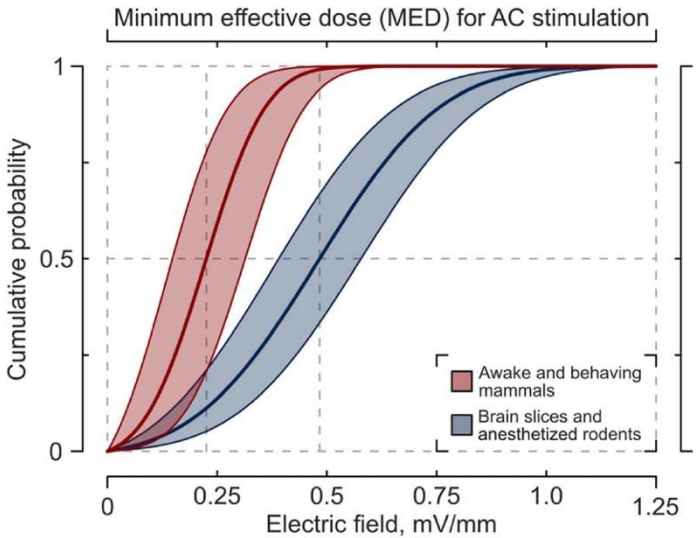
Violante *et al.* (2023) Nature Neuroscience

Interference

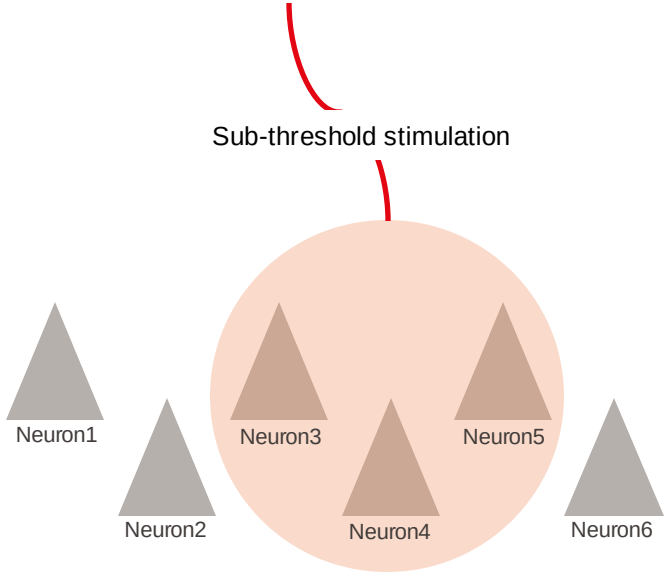


Vassiliadis *et al.* (2024) Nature Human Behavior

Co-activation



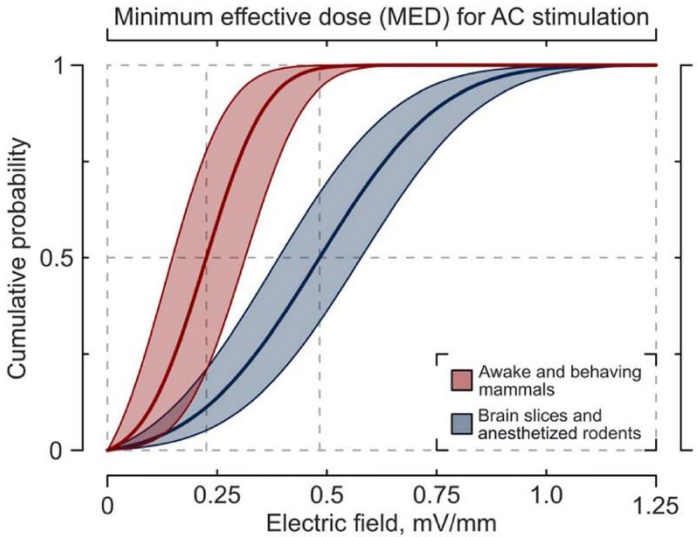
Alekseichuk, 2022



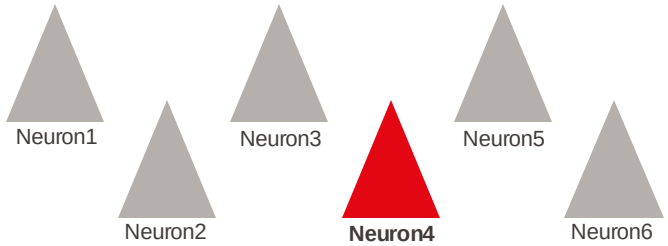
No stimulation effect

Subthreshold stimulation requires **co-activation** (Fritsch *et al*. 2010)

Co-activation

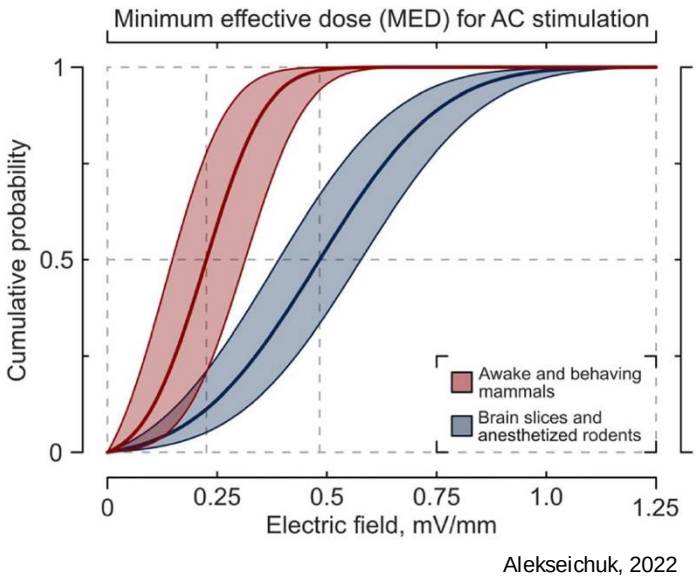


Alekseichuk, 2022

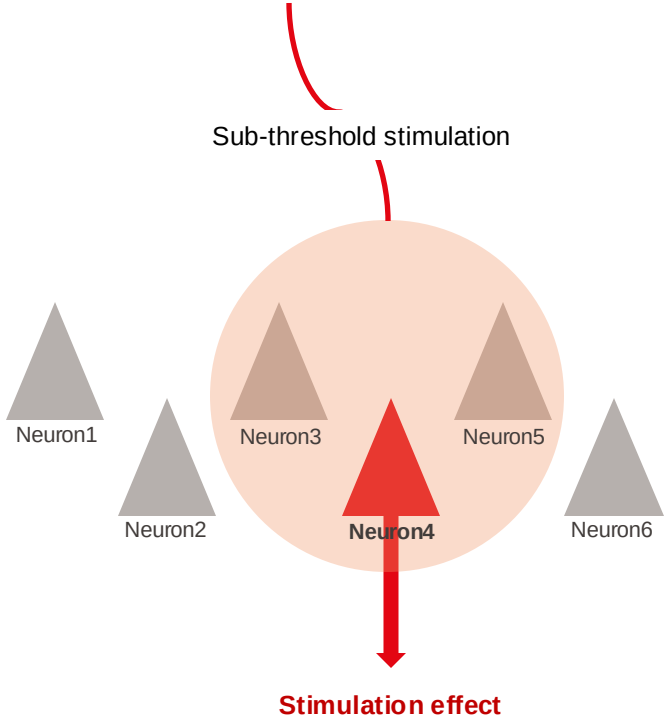


Subthreshold stimulation requires **co-activation** (Fritsch *et al.* 2010)

Co-activation



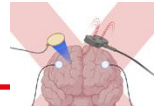
Alekseichuk, 2022



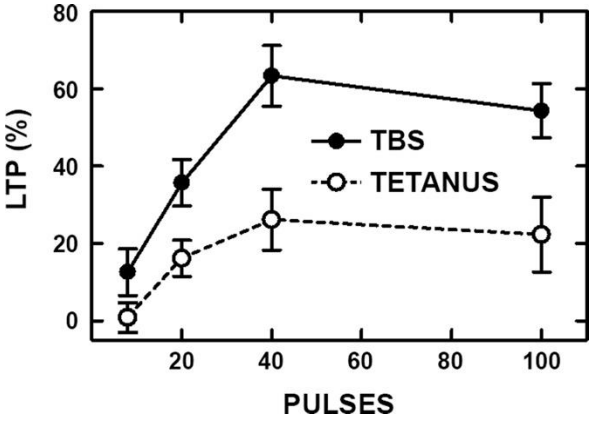
Subthreshold stimulation requires **co-activation** (Fritsch *et al.* 2010)

Co-activation **steers** the stimulation effects

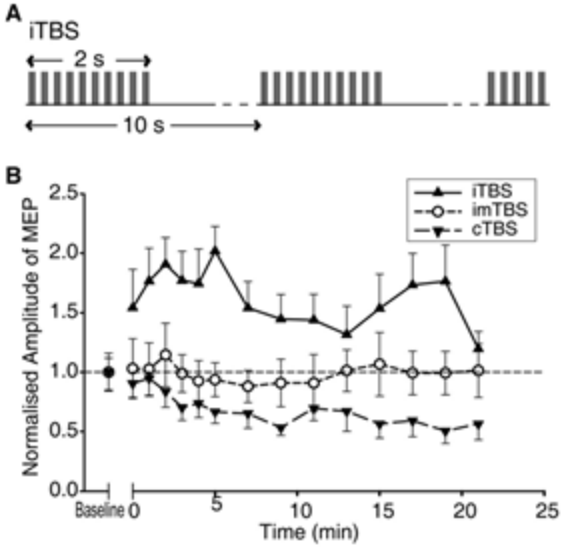
Theta burst stimulation (TBS)



Hippocampal field CA1



Larson& Munkasy 2015
Andersen 1991



Huang *et al.* 2005

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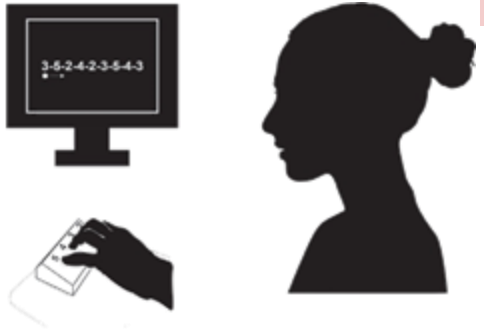
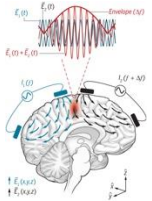
Striatum



Zimerman *et al.* 2013, 2014; Draaisma *et al.* 2022, Maceida *et al.* 2022; Wessel *et al.* 2023

Hippocampus

Moon *et al.* 2022



- **iTBS-TI**: 2 tACS channels @ 2kHz and 2.1kHz creating an interference wave with an envelope mimicking a theta-burst, with trains of 3 peaks @100Hz repeated every 200 ms applied for 2sec and followed by 8 sec of HF-control

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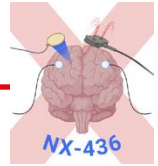
Theta burst stimulation (TBS)



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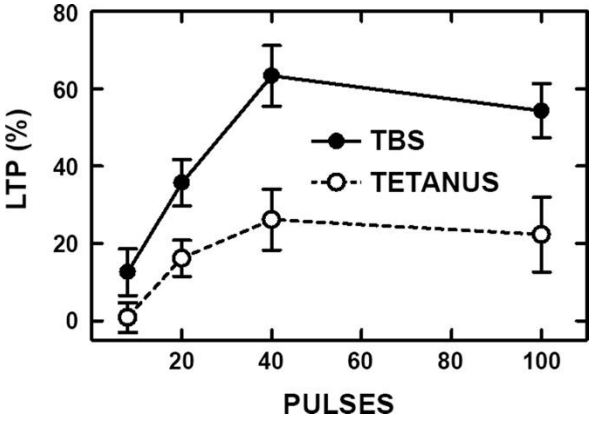
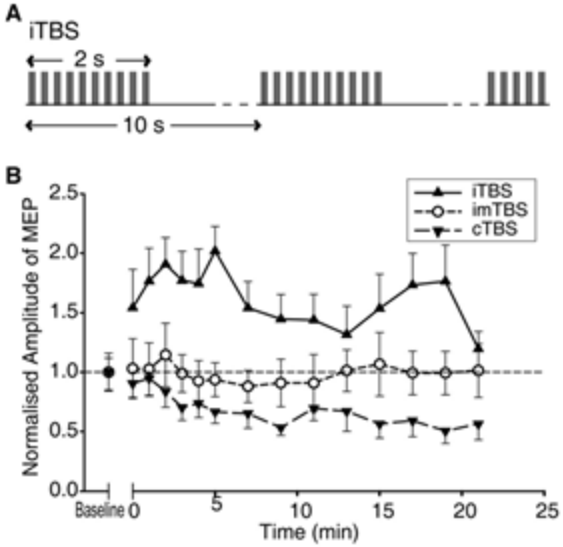


Larson& Munkasy 2015
Andersen 1991



Huang *et al.* 2005

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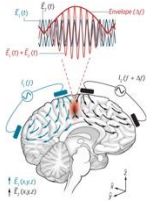
Striatum

Zimerman *et al.* 2013, 2014; Draaisma *et al.* 2022, Maceida *et al.* 2022; Wessel *et al.* 2023



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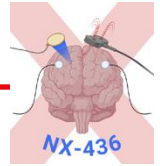
Neuroplasticity – iTBS tTIS



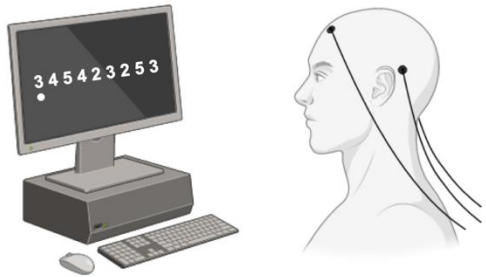
nature neuroscience

Article

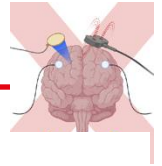
https://doi.org/10.1038/s41593-023-01457-7

Noninvasive theta-burst stimulation of the human striatum enhances striatal activity and motor skill learning

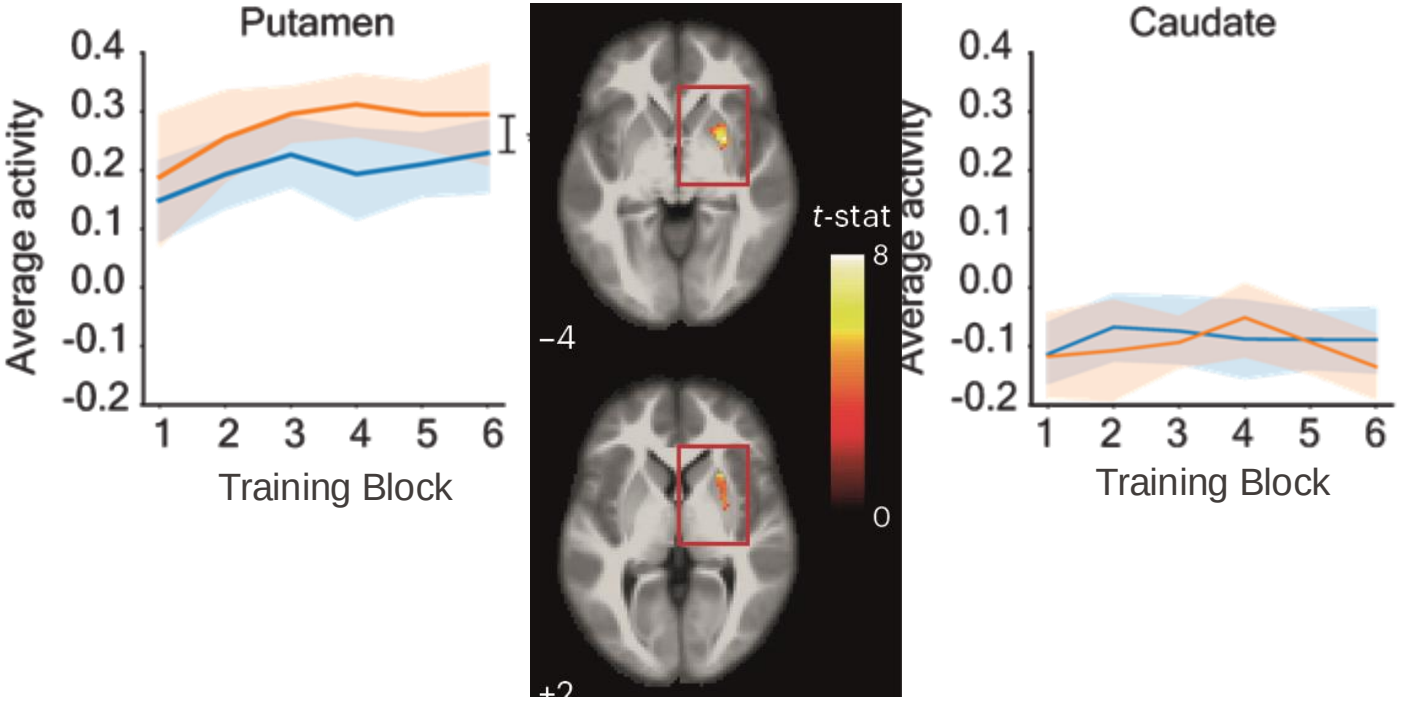
Wessel, Beanato *et al.* 2023



Topographic specificity of the stimulation effects



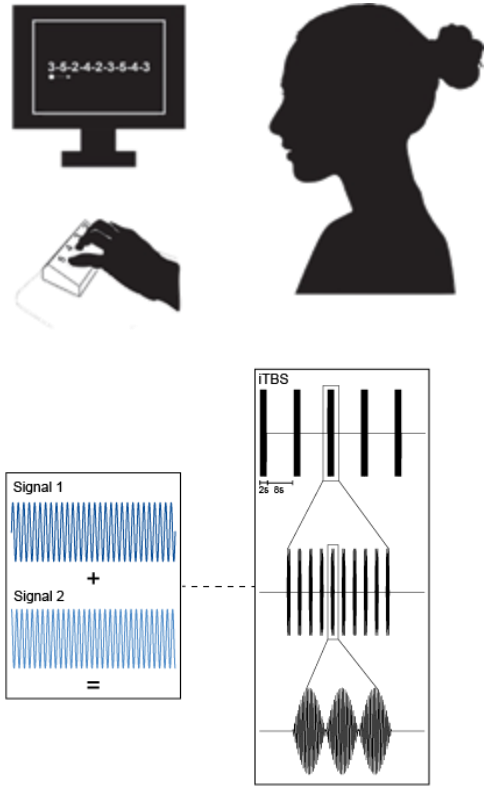
Associated with tTIS induced behavioral improvement

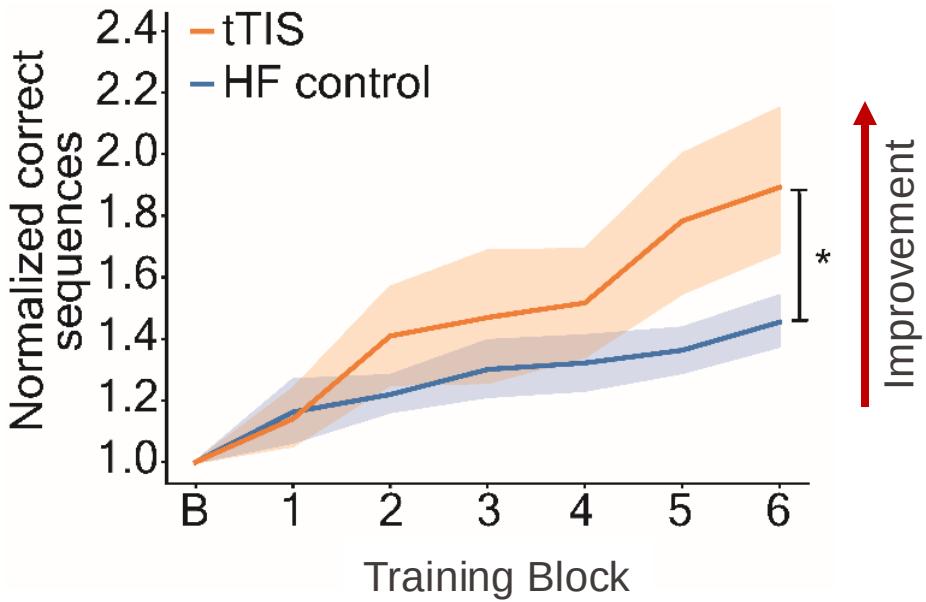


Stimulation effects are specific to the subregion already involved in the task

Wessel, Beanato *et al.* (2023) Nature Neuroscience

Validation striatal tTIS - healthy older



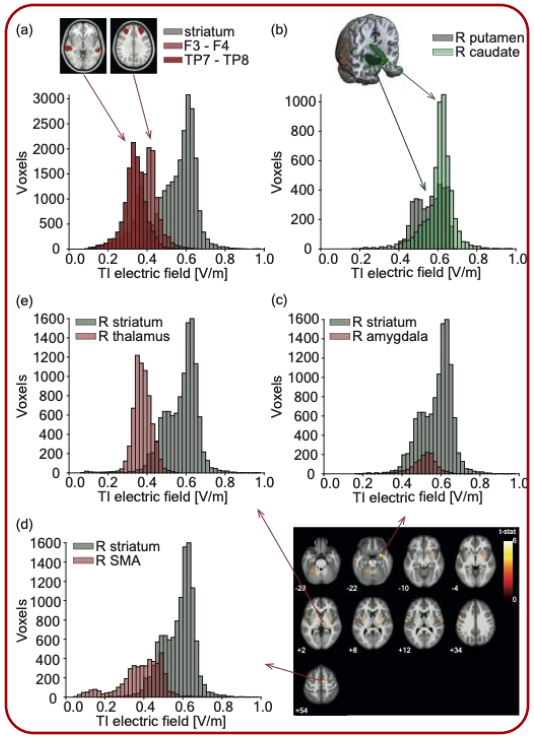


Striatal TBS-tTIS can modulate striatal activity and improve motor sequence learning

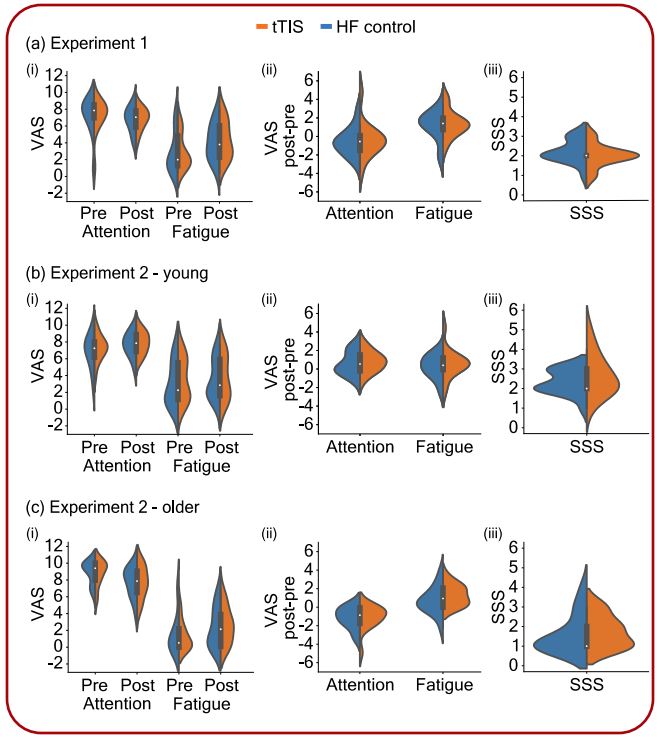
Wessel*, Beanato* et al., 2023, *Nature Neuroscience*

Potential influential factors

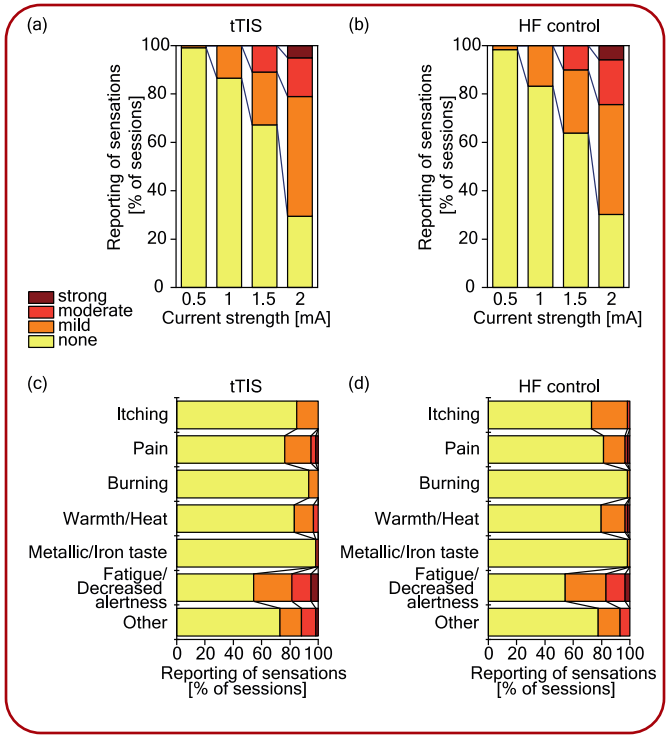
Focality of field strength



Attention, Fatigue



Perceived sensations



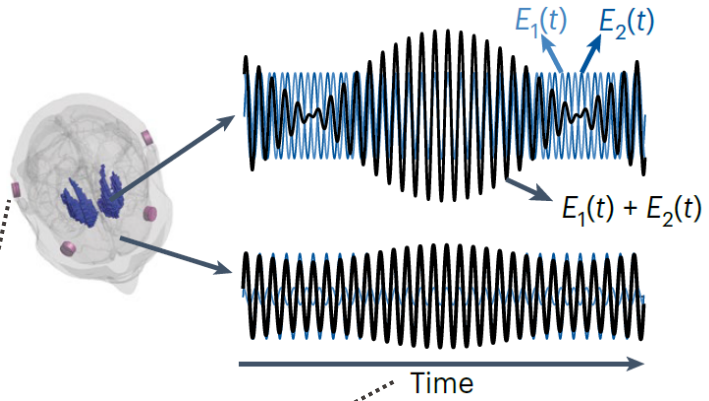
Wessel*, Beanato* et al., 2023, *Nature Neuroscience*

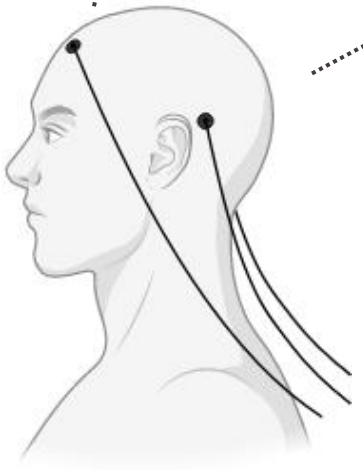
Striatal tTIS & Learning – Clinical proof of concept

15 TBI patients

3 female, 12 male

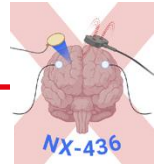
age: 52.67 ± 13.6





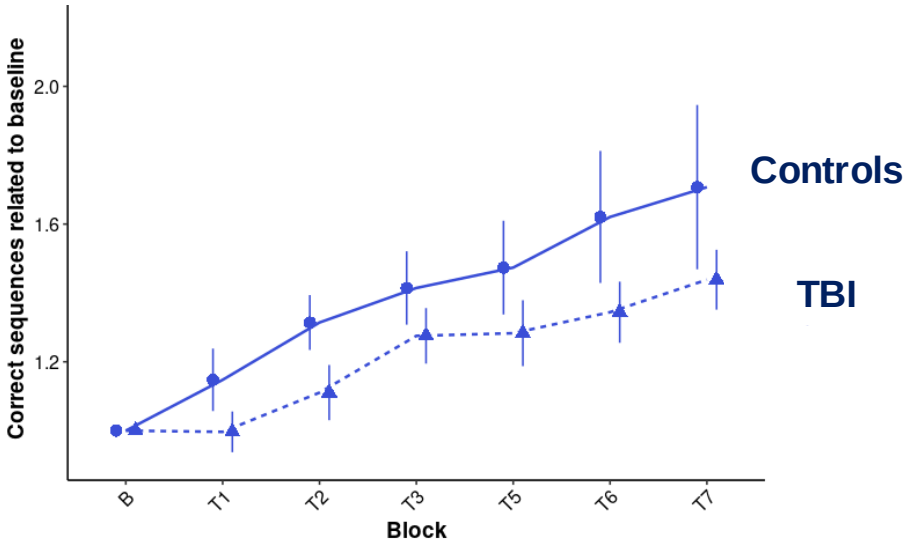
Plasticity-inducing protocol:

intermittent Theta Burst Stimulation (iTBS)



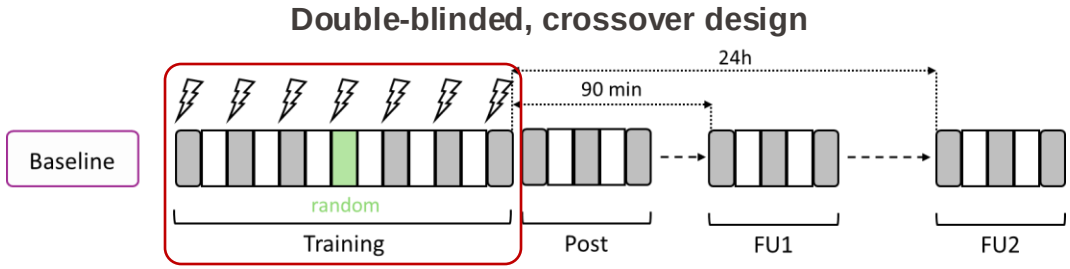
Ploumitsakou*, Beanato* *et al.*, in preparation

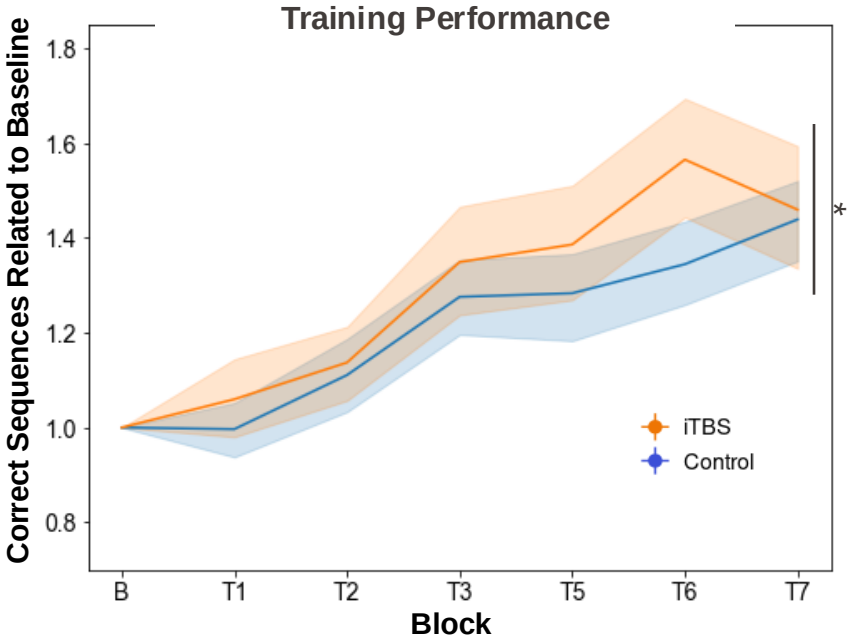
Enhancing Learning in TBI Patients



Ploumitsakou*, Beanato* *et al.*, in preparation

Enhancing Learning in TBI Patients





Ploumitsakou*, Beanato* *et al.*, in preparation

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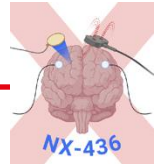
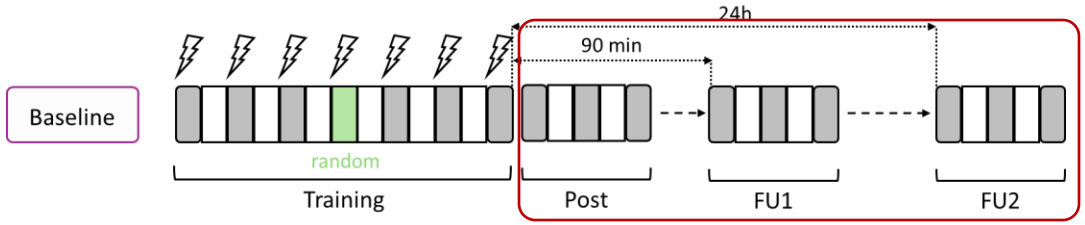
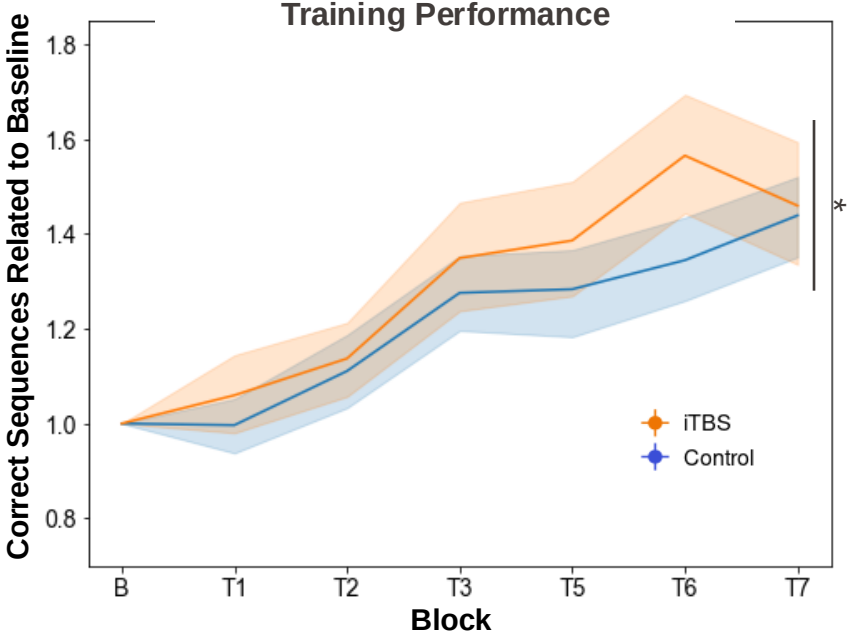


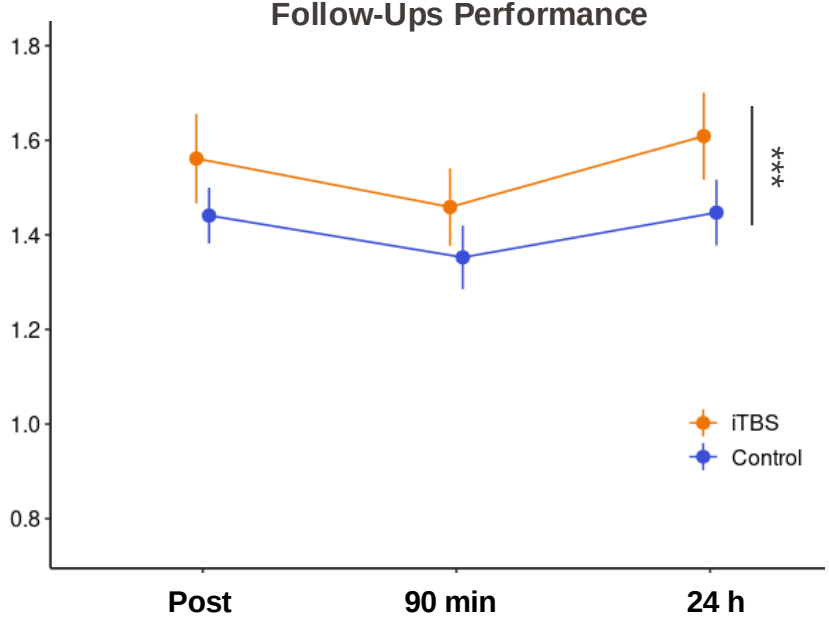
Double-blinded, crossover design



Training Performance

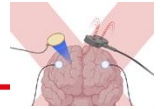


Follow-Ups Performance

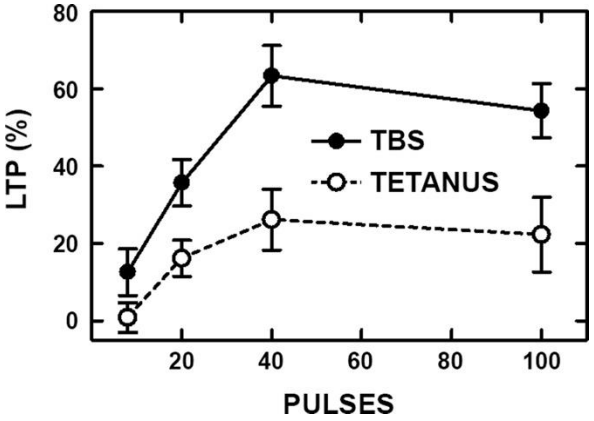


Ploumitsakou*, Beanato* *et al.*, in preparation

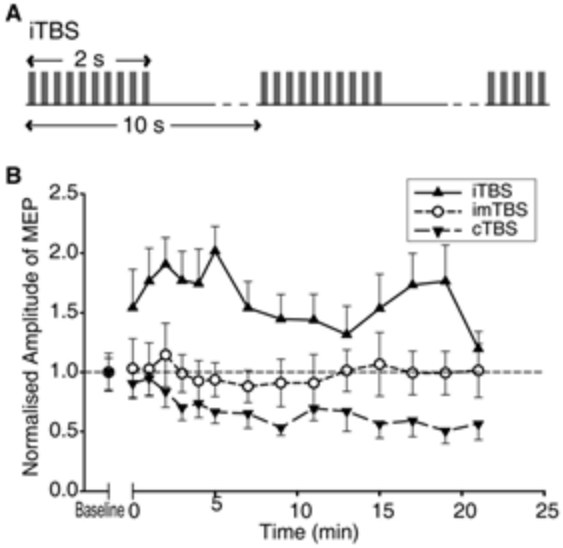
Theta burst stimulation (TBS)



Hippocampal field CA1



Larson& Munkasy 2015
Andersen 1991



Huang *et al.* 2005

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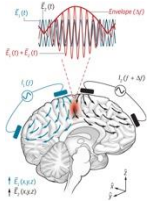
Hippocampus

Moon *et al.* 2022



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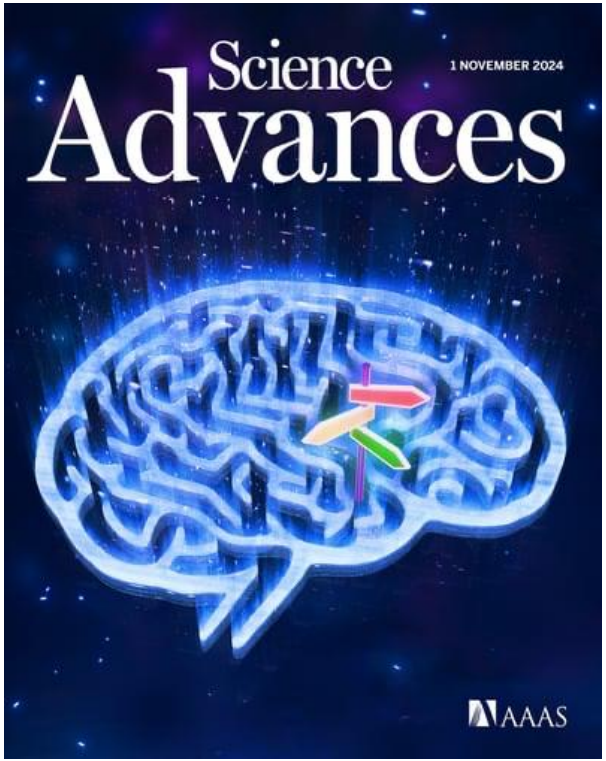
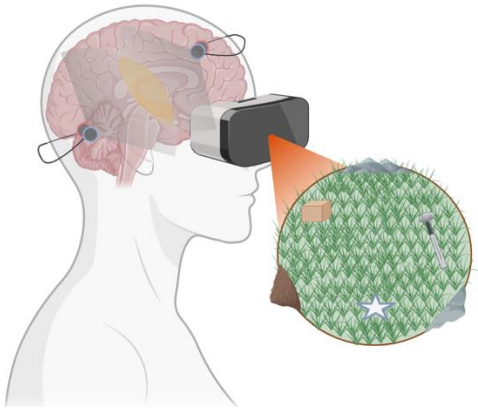
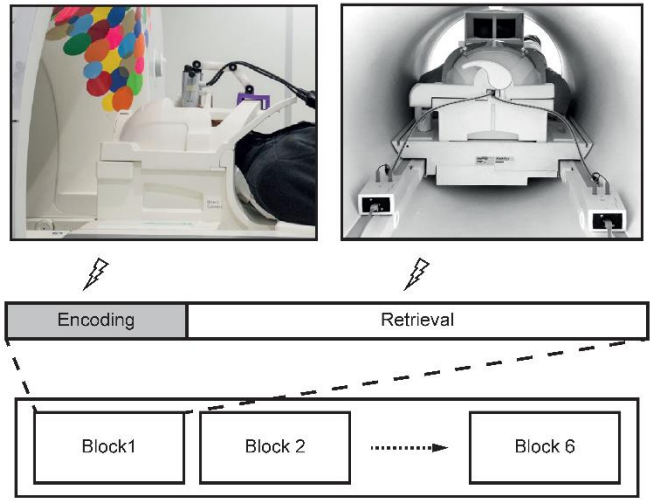
Non-invasive DBS - memory

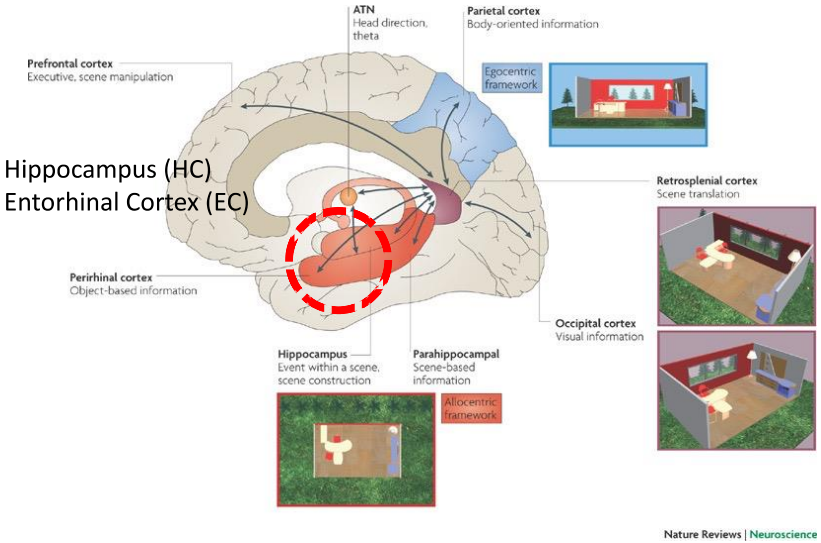






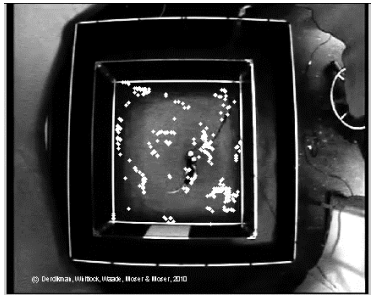
Beanato, Moon *et al. Science Advances* (2024)

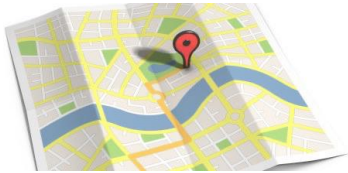
Plasticity-inducing tTIS during spatial memory



Hippocampus (HC)
Entorhinal Cortex (EC)

- Grid cells in Entorhinal cortex (EC)

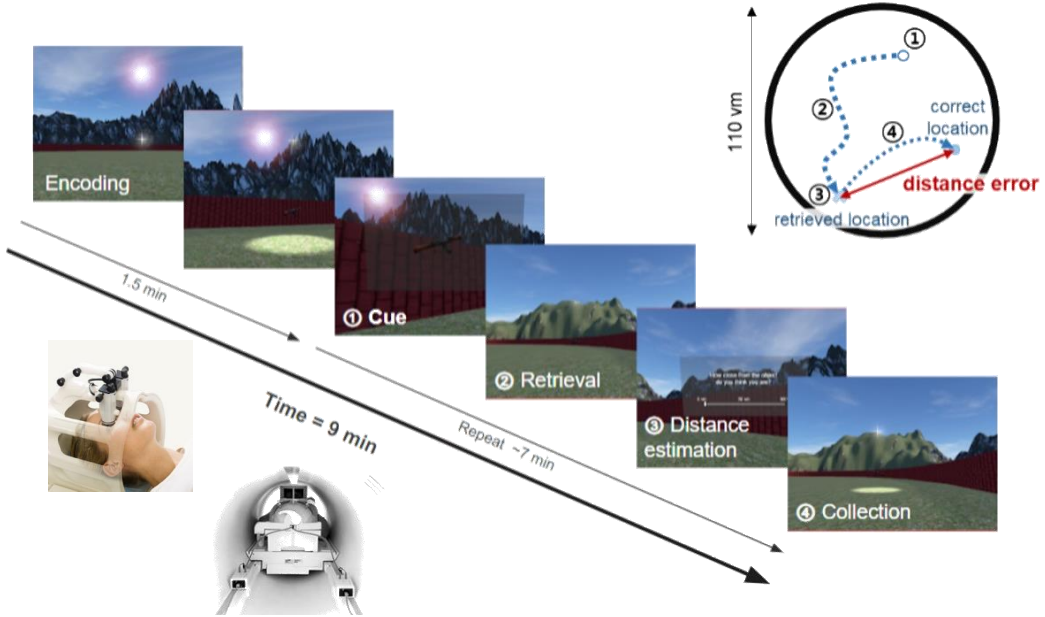




- allocentric spatial representation in the brain
- Spatial navigation
- Memory
- Alzheimer's disease (AD) /MCI

Vann et al., 2009; Moser et al. 2008; Byrne et al. 2007; Kunz et al., 2015

Plasticity-inducing tTIS during spatial memory

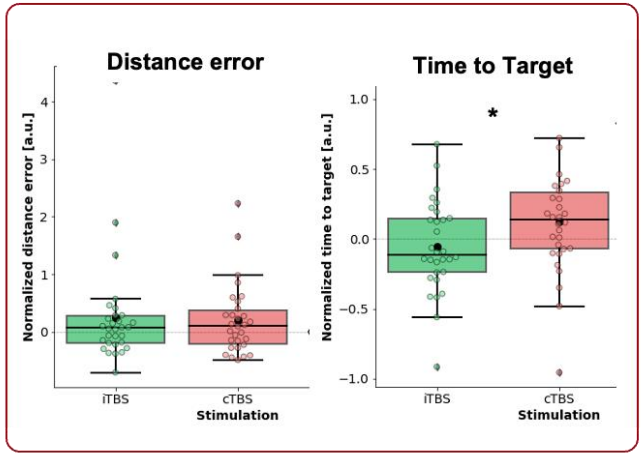


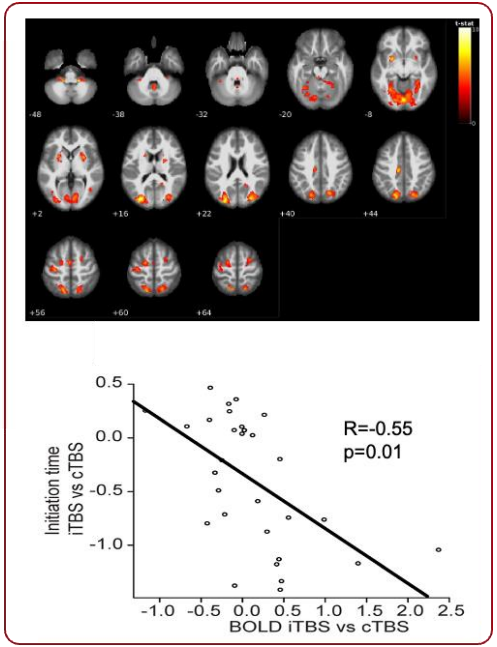
- N = 30 young healthy subjects
- Age 23.6 ± 4.07
- Randomized, double-blind design
- 6 blocks of ~ 9,5 min each
- A-B-C-C-B-A design
- Stimulation: **iTBS-TI** vs. **cTBS-TI** vs. **control** during encoding and retrieval phase
- Target: **right hippocampus**
- Instruction: “perform as **accurate** as possible”

Beanato, Yoon *et al.* (in prep)

Non-invasive DBS - memory

Spatial navigation



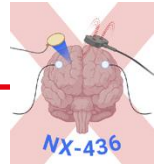


The bigger the hippocampal activity during verum nDBS vs control the faster subjects retrieve the information about where to go

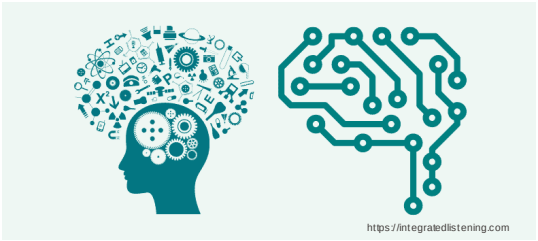
Non-invasive deep brain stimulation of the hippocampus enhances spatial memory
Opportunity to provide this treatment strategy to patients suffering from memory deficits

Beanato, Moon *et al. Science Advances* (2024)

Stimulation protocol

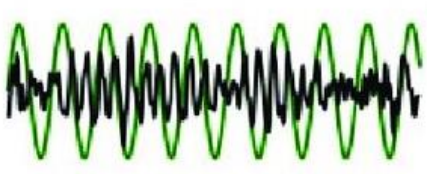


Neuroplasticity



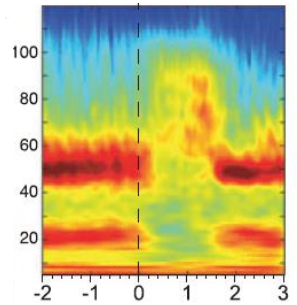
Wessel, Beanato *et al.* (2023) Nature Neuroscience
Popa, Beanato *et al.* (2023) bioRxiv
Beanato, Moon *et al.* (under review)

Neuronal entrainment



Violante *et al.* (2023) Nature Neuroscience

Interference



Vassiliadis *et al.* (2024) Nature Human Behavior

Interference

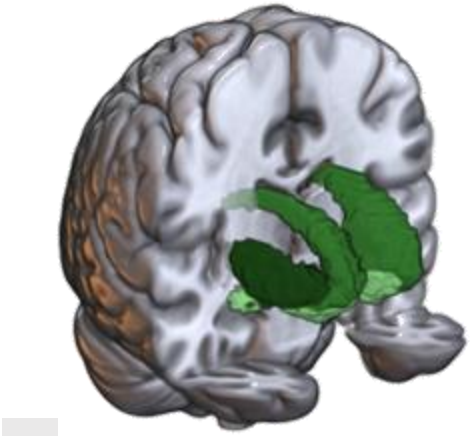
nature human behaviour

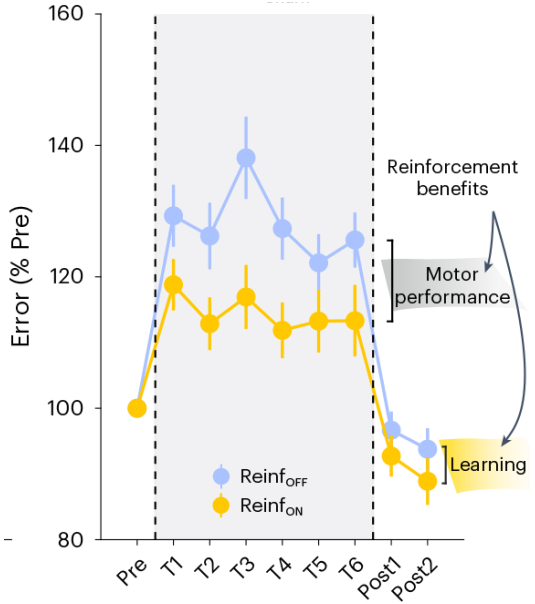
Article

https://doi.org/10.1038/s41562-024-01901-z

Non-invasive stimulation of the human striatum disrupts reinforcement learning of motor skills

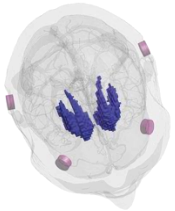
Vassiliadis *et al.* 2024





Causal role of the striatum – reinforcement learning?

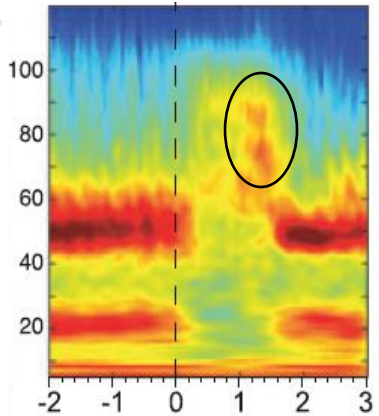
Striatum active in reinforcement learning (Bartra *et al.*, 2013) and motor learning (Hardwick *et al.*, 2013; Wessel, Beanato *et al.*, 2023)



Striatum suggested to be involved in the benefits of reinforcement on (motor) learning

Specific oscillations in the striatum associated to different functions:

- **Beta** (~20Hz) ⟺ sensorimotor control (Jenkinson et al., 2013)
- **High gamma** (~80Hz) ⟺ reward processing (Berke, 2009)



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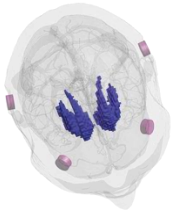

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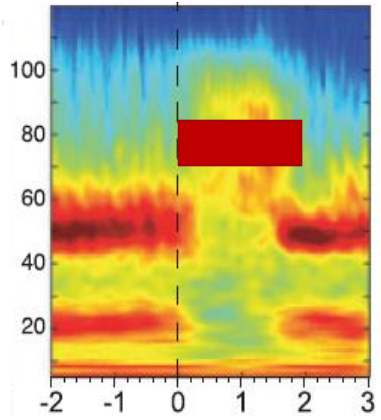


Reward will be disrupted

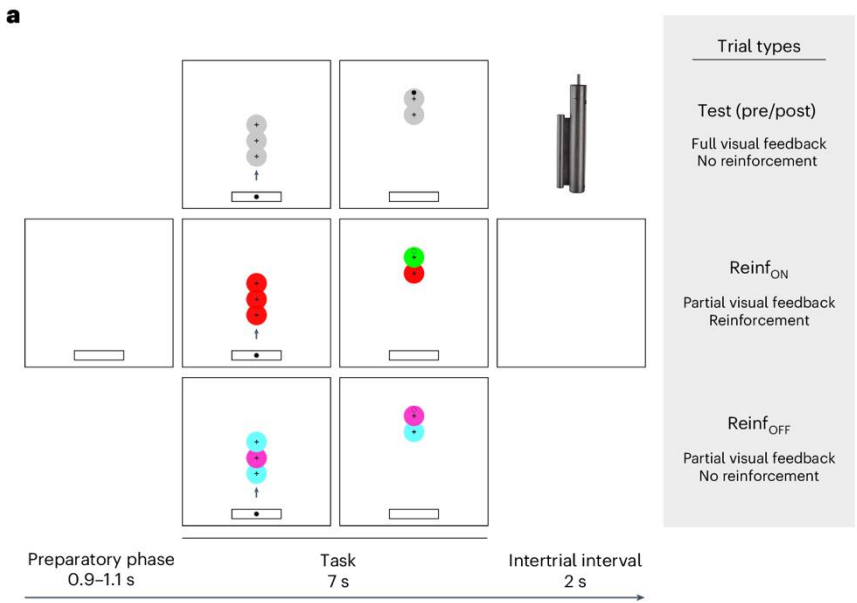
No Reward

Hypothesis:

Continuous, open-loop **striatal** stimulation at **80Hz** will **perturb** the **reinforcement-dependent** regulation of high gamma oscillations and **disrupt** the benefits of reinforcement on learning

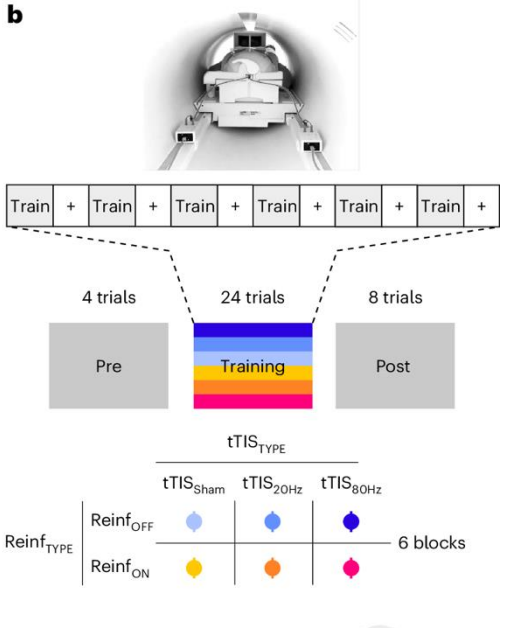
Experimental set up

Renforcement Learning



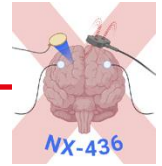
Vassiliadis *et al., 2021, 2022* iScience

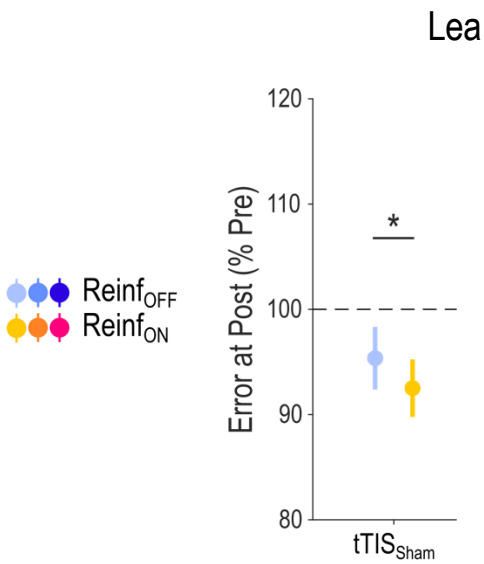
tTIS + task concomitant with fMRI



Vassiliadis *et al., 2024* Nature Human Behavior

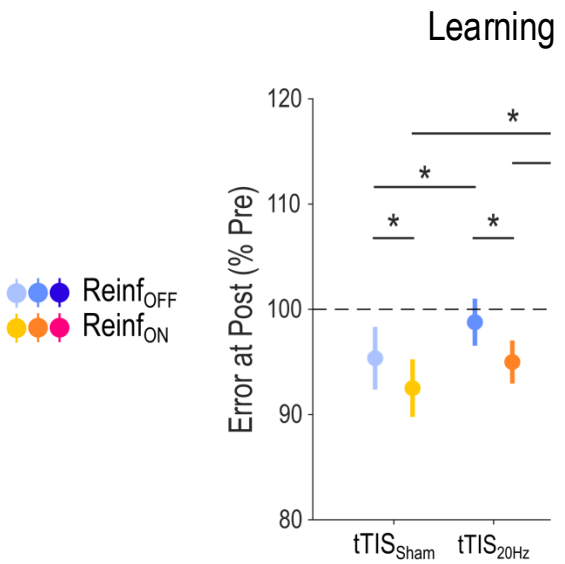
Results - Behaviour





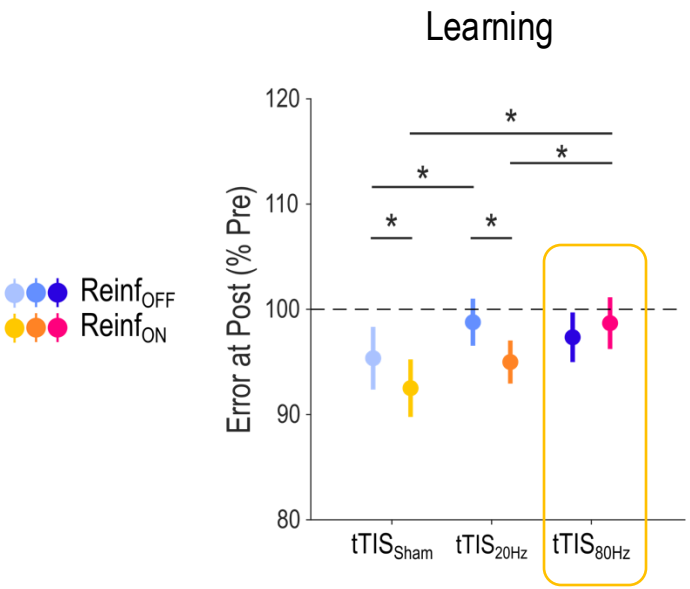
Vassiliadis *et al., 2024* Nature Human Behavior

Results - Behaviour



Vassiliadis *et al., 2024* Nature Human Behavior

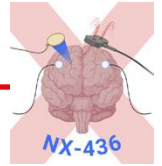
Results - Behaviour

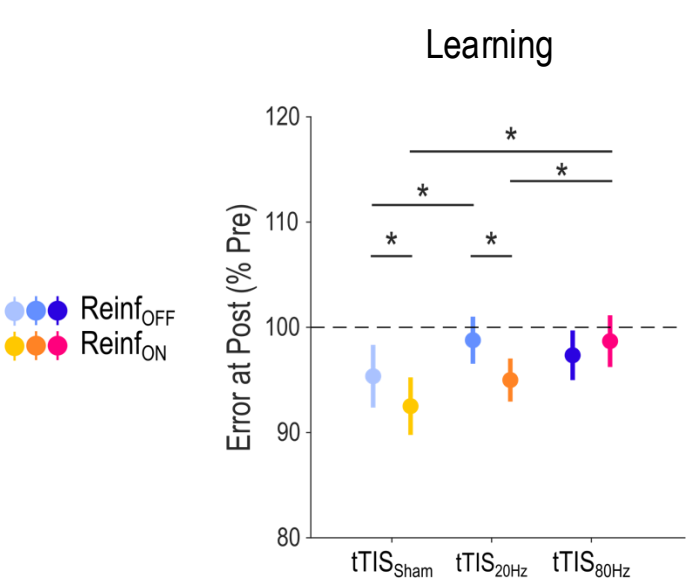


→ **tTIS$_{80Hz}$ disrupts** the benefits of **reinforcement** on motor learning, not motor learning in general

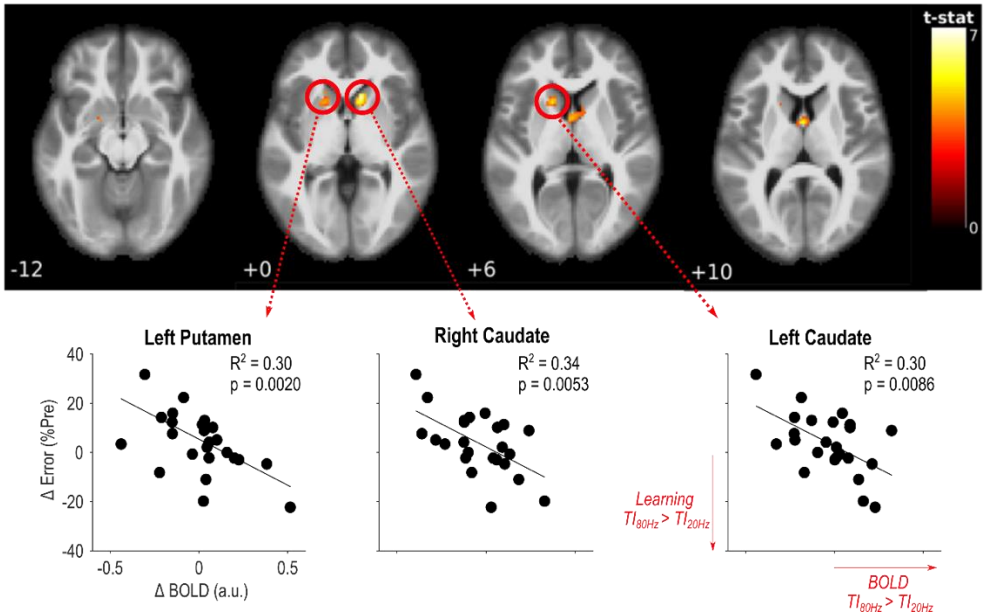
Vassiliadis *et al., 2024* Nature Human Behavior

Results – Behaviour + fMRI





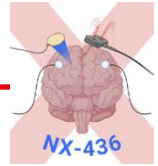
tTIS$_{80Hz}$ – tTIS$_{20Hz}$ contrast; Reinf$_{ON}$



→ **tTIS$_{80Hz}$ disrupts** the benefits of **reinforcement** on motor learning, not motor learning in general

Disruption of reinforcement motor learning with tTIS$_{80Hz}$ **correlates with changes of neural activity in the striatum**

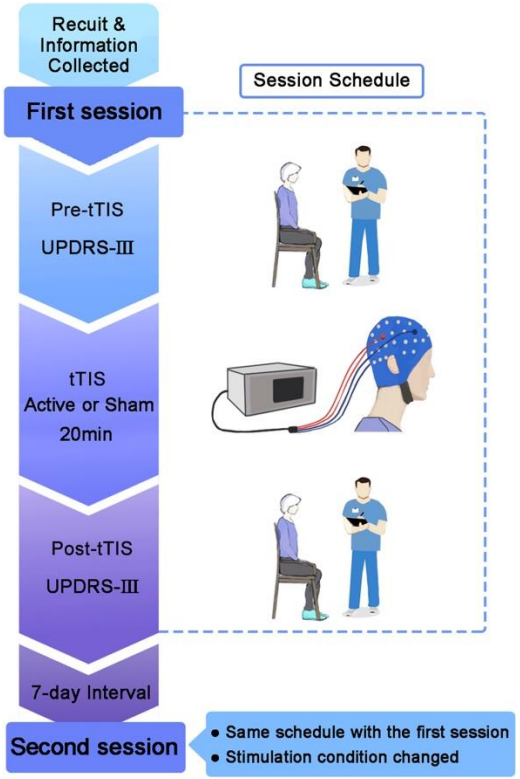
Vassiliadis *et al., 2024* Nature Human Behavior

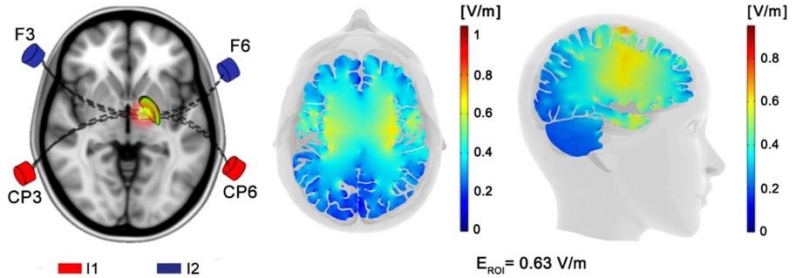


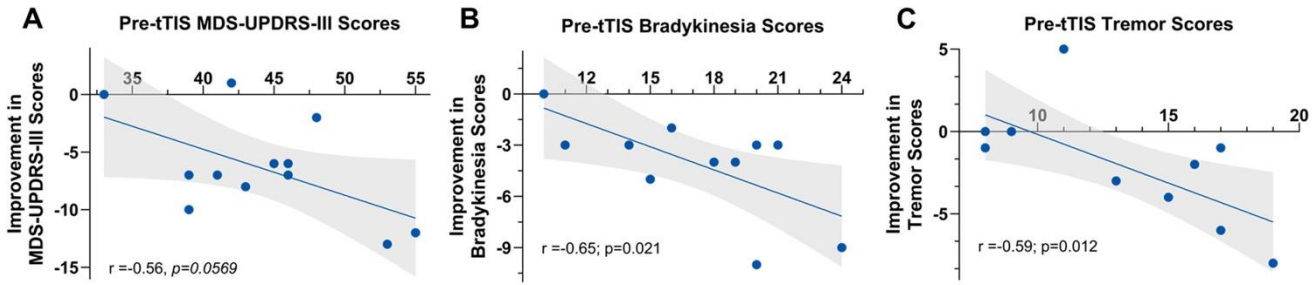
Clinical translation – Parkinson's

Clinical translation – Parkinson's

Unilateral STN 130Hz tTIS



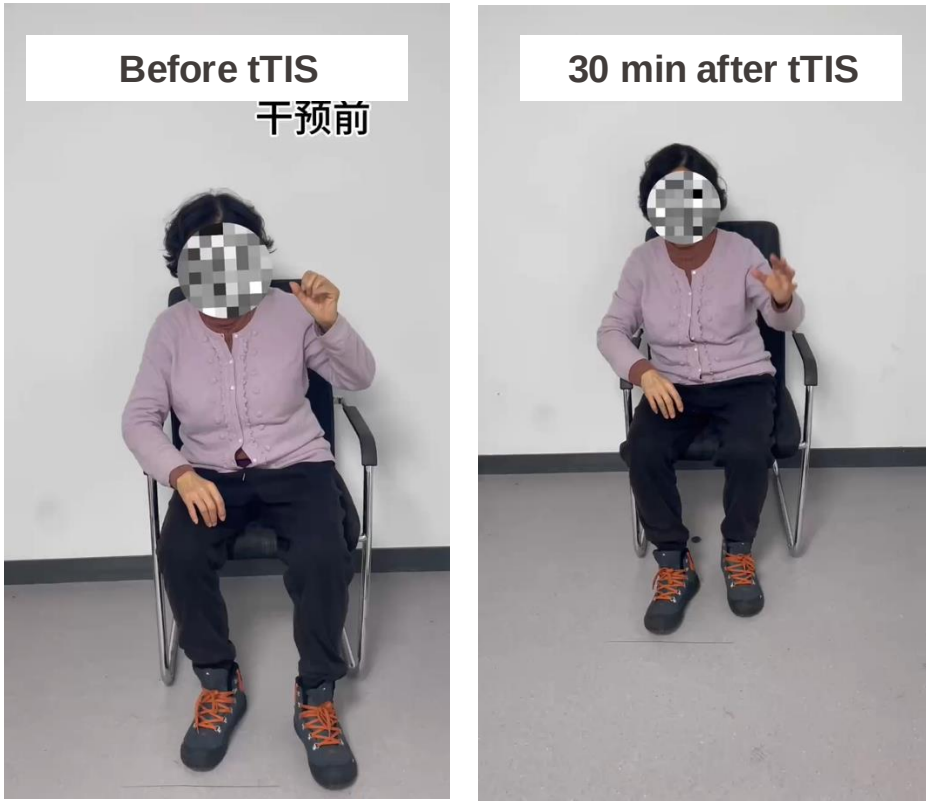




Yang et al. 2024 MDS

Clinical translation – Parkinson's

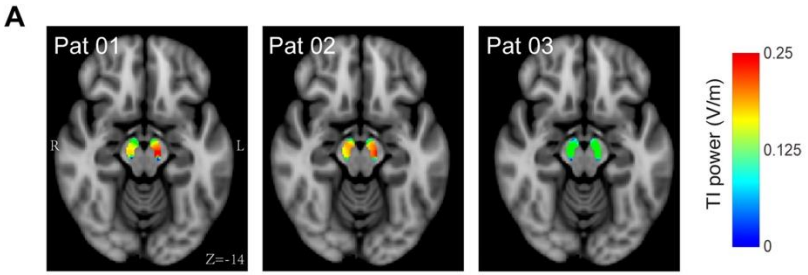
Unilateral STN 130Hz tTIS

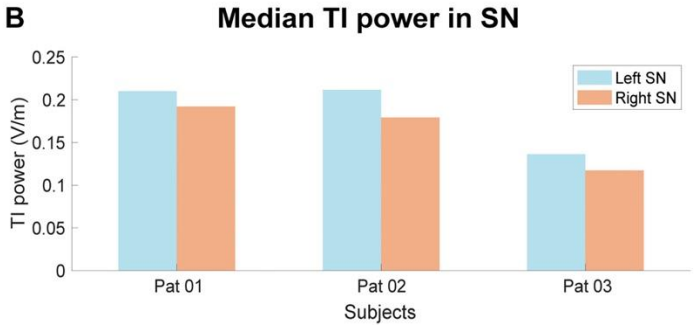


Courtesy from Prof. Chencheng Zhang (Shanghai)

Clinical translation – Parkinson's and Essential Tremor

Bilateral STN
130Hz tTIS





The pilot results of TI treatment in motor disorder.

#Patient	Diseases	Gender	Age (years)	On-line/ off-line	Stimulation duration	Total current intensity	Improved item (compared to baseline)	The change of score (baseline→during/after TI)
Pat 01	ET	Female	57	Off-line	20 min	2 mA	Continuity of resting tremor	2→1
Pat 02	PD	Female	70	On-line	~10 min	2 mA	Continuity of resting tremor	3→1
Pat 03	PD	Female	59	On-line	~10 min	1.5 mA	Amplitude of resting tremor (right upper limb)	2→1

The score 1 in continuity (Pat 01/02) of resting tremor refers to the time of tremors accounting for less than 25 % of the total assessment time, the score 2 refers to 26 % ~50 %, the score 3 refers to 51 %~75 %; The score 1 in amplitude (Pat 03) of resting tremor refers to the amplitude smaller than 1 cm, the score 2 refers to 1–3 cm. ET, essential tremor; PD, Parkinson's disease.

Liu *et al.*, *2024* NIMG

Summary

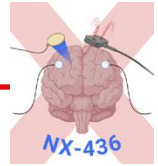
- Novel innovative neurotechnology extends the use of orchestrated non-invasive brain stimulation to deep brain structures (hippocampus, basal ganglia)

- Temporal Interference stimulation (**tTIS**) provides a **promising** opportunity to neuromodulate **non-invasively deep** brain structures like the
  - striatum (Wessel, Beanato *et al.* 2023 Nature Neuroscience; Vassiliadis *et al.* 2024 Nature Human Behavior)
  - hippocampus (Violante *et al.* 2023 Nature Neuroscience; Beanato, Yoon *et al.* 2024 Science Advances)
  - first applications in patients (TBI, Ploumitsakou *et al.* in prep; Parkinson, Liu *et al.* 2024; Zhang et al. 2024)

- Opens new promising **opportunities** for **novel non-invasive interventional strategies** for **neurological** and **psychiatric** disorders targeting deep brain structures involved in the pathophysiology or in the recovery process of the disorders
  - TBI or Stroke
  - Parkinson's
  - Dementia
  - Anxiety, Addiction
  - Apathy or Fatigue

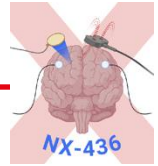
- Next steps require further technological development and acquisition of strong clinical evidence

- Translation into daily clinical life



Open questions, challenges

- Parameter space (frequency)
- Higher topographic resolution
- Understanding of underlying mechanisms
- Personalized application
- Closed-loop stimulation
- Home-based self-application
- Proof-of-concept in clinical populations



Questions?